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Attorneys for Debtor
SARA NEWSOME BURNS

UNITED STATES BANKRUPTCY COURT

SOUTHERN DISTRICT OF CALIFORNIA

In re:

SARA NEWSOME BURNS, an individual,

Debtor.

CASE NO. 99-33191-B7

DECLARATION OF SARA NEWSOME BURNS IN OPPOSITION TO MOTION OBJECTING TO DEBTOR'S AMENDED EXEMPTION CLAIM

Date: May 30, 2000
Time: 11:00a.m.
Dept: 4
Hon. Peter W. Bowie

I, Sara N. Burns declare as follows:

1. I am over the age of 18 and the Debtor in this bankruptcy case.

2. My date of birth is February 4, 1958. I was born with a physical anomaly known as Hip Dyplasia.

3. As a result of this condition, which was exacerbated by injuries I suffered in a serious automobile accident in 1990, I am now permanently, and fully disabled. I have undergone ten (10) hip replacement procedures beginning in 1971, when I was 13 years old, and the last of which was in 1994.

4. I was first recognized as qualifying for disability assistance in 1993. At that point I received full disability payments from the State of California. However, those disability entitlements

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had a one year duration which expired in 1994.

5. In 1994, after my ninth hip replacement surgeries, I formally became qualified for social security benefits based upon my total disability. From that point, to the present, I have continued to receive social security benefits for my disability. Attached to this Declaration marked as Exhibit 1, is a copy of the form SSA-1099- social security benefit statement which I received from the office of Social Security Administration in or about January 2000 (the "1099"). This 1099 form accurately summarizes the amount of my disability benefits provided by the Social Security Administration in the calendar year 1999.

6. In January 2000, I received a notice from the Social Security Administration notifying me that I would receive a 2.4% cost of living increase in my disability benefits for the calendar year 2000. I have attached to this Declaration marked as Exhibit 2, a copy of that notification.

7. The following is a summary of the surgical procedures and events which have culminated in my total and permanent condition of disability:

7.1 As I said earlier, the first surgical procedure I underwent in an attempt to correct my Hip Dysplasia occurred when I was 24 months old. That was not a hip replacement procedure, but a surgical procedure intended to correct or improve the condition. From that point on I underwent a series of surgical procedures involving traction for approximately two months followed by open reductions and being placed in a body cast for three months at a time attempting to correct or improve the Hip Dysplasia approximately once a year, until I reached the age of 13. At which point I had my first hip replacement procedure.

7.2 **1971**. At the age of 13, I underwent a bilateral hip replacement procedure. As the name suggests, both of my natural hip joints were replaced during that procedure.

7.3 **Circa 1979.** In my early 20's I again underwent hip revision surgery for my right hip. Each of these procedures, in fact all of the hip replacement and revision procedures that I am describing in this Declaration, required between 7-10 hours of surgery to complete the procedure.

7.4 **Circa 1983.** At this time, difficulties in the earlier procedures require that I once again undergo hip replacement surgery to my left hip.

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7.5 **Circa 1985.** At the age of 27, I once again had to undergo a bilateral hip replacement surgical procedure.

7.6 **July 1990.** At this time I was involved in a serious automobile accident. The car that collided with mine struck my vehicle "broadside" at or about the location of the door next to the seat that I occupied. That vehicle struck mine with such force that it drove my door into me, crushing my left hip and requiring its surgical replacement/reconstruction which took place in 1996.

7.7 **Circa 1991.** Follow up hip replacement surgery was required because of complications from the automobile accident. I awoke with paralysis in my left hip, had foot drop and had difficulty with my balance. Because of the paralysis in my left hip, I now suffer with a back problem and neck pain due to the imbalance of my gait as a result of the various surgeries, resulting over compensations in movement and posture.

7.8 **Circa 1993.** After my back went out it was discovered that hip prosthesis failed, and I was diagnosed as having both hips in a disconnected condition. I was again experiencing problems resulting from the prior hip replacement surgeries. At this time I underwent a hip replacement procedure for my left hip which utilized a prosthetic device which was described to me as "*experimental*" at the time.

7.9 **July 1994.** As a result of that condition I underwent my ninth bilateral hip replacement surgery. Because I had been significantly weakened by prior surgeries and suffered substantial muscle atrophy, I was in a full body cast for six weeks following that surgery.

7.10 In **December 1994.** I underwent my 10th replacement on my right hip. Because there is very little bone left in my hips, there was difficulty in properly aligning the hip and it is not completely attached to the bone- this causes popping in my hip at times because it is not properly placed. I'm told by my doctors that this condition may need future surgery to correct. Although it was discussed that I could have it corrected at that time the rest of my body was placed into such a weakened state that I felt that I could not undergo the additional trauma of surgery at that time. I do not believe that I have sufficiently recovered my stamina to have the corrective surgery performed as of yet.

7.11 As a result of a transfusion I received in connection with one of my surgeries,

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I contracted Hepatitis C. I have been treated for that condition. It has been diagnosed as chronic, and this past year the symptoms of my condition have become exacerbated. My present symptoms include right side pain, vomiting- sometimes up to eight times a night, nausea and extreme fatigue. Lisa Nyberg, M.D., the doctor who diagnosed me as having the chronic Hepatitis C condition, provided me with a 62 page pamphlet concerning issues that I should be aware of in connection with this disease. I have attached a copy of that document to this Declaration as Exhibit 3.

7.12 In **late 1999** I developed severe headaches. My general physician Anne Stewart, M.D., referred me to Dr. Murray A. Richter, a radiologist, to perform a magnetic renascence imaging diagnostic test of my brain. I have attached a copy of his preliminary findings as Exhibit 4 to this Declaration.

8. At the present time, and at the time that I filed my bankruptcy petition in this Chapter 7 case, my physical conditions prevent me from obtaining a job of any kind. Although I have in the past worked as a nurse's aid, a practical nurse, and a billing clerk for various doctors my condition has deteriorated with my surgeries and the onset of Hepatitis to the point where I can no longer work. What follows is a summary of my employment history:

8.1 **Circa 1976.** I then resided in Illinois and began working as a nurse's aid. At the same time, I was attending Parkland Junior College from which I obtained a certificate qualifying me to work as a practical nurse.

8.2 **Circa 1981.** I began working full time as a practical nurse. I took course to become a registered nurse, but was not able to complete that course of study.

8.3 **Circa 1986.** The surgeries I had received to that point began to impair my ability to effectively perform my functions as a practical nurse. At that time, my doctors advised me to "*give up floor nursing*", indicating that I would be unable to effectively perform those functions in the future. At that point, I accepted a position as a "*utilization review coordinator*". That is an analyst function where the coordinator reviews patient charts and makes recommendations for future treatments/discharge and ensures that the recommendations are consistent with the hospital's "*cost containment*" policies. This change of position- from a practical nurse to a utilization review coordinator- was not a "*career enhancement*". It did not have the same opportunities for advancement

and potential for earnings that I would have had as a practical nurse. Rather, I made that change simply as a necessary accommodation to the realities of my physical limitations resulting from my Hip Dysplasia and the various surgeries I had undergone at that point. Later, I left that work and was able to obtain employment as an office manager for various physicians. However, because the pay level was so low I generally needed to hold at least two such positions at a time, and work 12 hour days, in order to earn a basic living in that function. I continued in that capacity from 1991 to 1993.

8.4 **Circa 1993.** At this point I worked as a billing clerk for a physician here in San Diego (Dr. Masters). However, my physical stamina was reduced and I was only able to work 30 hours a week in that capacity. Following my four hip replacement surgeries from 1991 through 1994, I have been unable to maintain full time employment. I did work in a clerical capacity for a "temp" agency in 1994. However, as a consequence of the various surgeries, and fatigue that I have as a result of the Hepatitis I am not able to sit for more than two hours at any given time. Additionally, I am not able to work in accordance with any predesignated work schedule because the effects of the surgeries, the Hepatitis, and the various medications, create circumstances where, and I often require a great deal of bed rest and inactivity. These episodes tend to occur randomly, and I simply cannot maintain the commitments that any employer would reasonably require. I actually tried to resume part time employment in early 1999. For three months I worked again as a temp, doing various bookkeeping functions. However, for the reasons I describe above I was unable to continue and could not now obtain employment in that capacity.

9. Most recently, on March 29, 2000, John G. Rowe, M.D., my orthopedic surgeon, confirmed that my severe cervical myalgia and bilateral hip osteoarthritis, made my physically unsuitable for Jury Duty. I have attached as Exhibit 5 to this Declaration a copy of the letter he wrote on my behalf to disclose that aspect of my physical condition. At or about that time I submitted a copy of Dr. Rowe's letter in support of my formal request to be excused from Jury Duty. Thereafter, I was not required to serve as a juror.

10. At this point, I am continuing to receive full disability benefits from Social Security Administration. That, and the modest income I receive from my "renter" who occupies the back portion of my home is the only income that I receive.

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11. I have first hand knowledge of the foregoing, and if called as a witness could, and would, testify as I have in the foregoing declaration.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 1st day of May, 2000, at San Diego, California.

Sara N. Burns

SARA N. BURNS

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SOCIAL SECURITY ADMINISTRATION
OFFICE OF CENTRAL OPERAT. S
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BALTIMORE MD 21241-1500

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AUTO
SARA J BURNS
4621 KENSINGTON DR
SAN DIEGO CA 92116-3824

Form SSA-1099-SM (1-2000)

U.S. Government Printing Office 1999-451-883

Printed on recycled paper

1099 A35675606 P000L 0000 -P1043

KEEP THIS FORM FOR PROOF OF SOCIAL SECURITY BENEFITS

IMPORTANT: TAX INFORMATION ENCLOSED

EXHIBIT 1

FORM SSA-1099 — SOCIAL SECURITY BENEFIT STATEMENT

1999 • PART OF YOUR SOCIAL SECURITY BENEFITS SHOWN IN BOX 5 MAY BE TAXABLE INCOME.
• SEE THE REVERSE FOR MORE INFORMATION.

Box 1. Name	Box 2. Beneficiary's Social Security Number
SARA J BURNS	354-56-0231

Box 3. Benefits Paid in 1999	Box 4. Benefits Repaid to SSA in 1999	Box 5. Net Benefits for 1999 *(Box 3 minus Box 4)*
$9,390.00	NONE	$9,390.00

DESCRIPTION OF AMOUNT IN BOX 3

Paid by check or direct deposit	$8,764.00
Medicare premiums deducted from your benefit	$546.00
Deductions for work or other adjustments	$80.00
Total Additions	$9,390.00

DESCRIPTION OF AMOUNT IN BOX 4

NONE

Box 6. Voluntary Federal Income Tax Withheld

NONE

Box 7. Address

SARA J BURNS
4621 KENSINGTON DR
SAN DIEGO CA 92116-3824

Box 8. Claim Number *(Use this number if you need to contact SSA.)*

354-56-0231A

Form SSA-1099-SM (1-2000)

DO NOT RETURN THIS FORM TO SSA OR IRS

EXHIBIT 1

FACTS ABOUT YOUR 1999 SOCIAL SECURITY BENEFIT STATEMENT

Your 1999 Social Security Benefit Statement is on the back of this form. Use it, along with the information below, to see if part of your Social Security benefits may be taxable.

What You Need To Do

Use the 1999 statement on the reverse, with the Internal Revenue Service (IRS) Notice 703 below, to see if any of your Social Security benefits are taxable. Do not return this form to us or the IRS. Do not attach it to your income tax return. We also are sending this benefit information to IRS. We did not include your SSI benefits, if any, on this statement. You may wish to keep this statement as proof of your income for use with public assistance. If you do not receive public assistance and you do not owe taxes on your Social Security benefits, you may ignore this form.

Who Receives This Statement

We must, by law, send you a statement that shows the Social Security benefits you received or repaid in 1999. We send separate statements to each person when we combine your check with another person's check. If you get more than one check each month, we may send you more than one statement.

Explanation of Items

Box 1–"Name"– shows the name of the person for whom we paid benefits.

Box 2–"Social Security Number"– shows the Social Security number of the person shown in Box 1, if we have the number.

Box 3–"Benefits Paid in 1999"– shows the total amount of Social Security benefits we paid you in 1999. This amount may not agree with the payments you actually received in 1999. The total we show includes amounts withheld to pay Medicare Part B premiums, etc. Our total also excludes some payments IRS does not tax. These items are listed in the "Description of Amount in Box 3." We included, in a separate column, payments we made in 1999, but for earlier years.

Box 4–"Benefits Repaid to SSA in 1999"– shows the total amount of benefits you repaid us in 1999. We show items that apply to you in the column headed "Description of Amount in Box 4."

Box 5–"Net Benefits for 1999"–shows the amount in Box 3 minus the amount in Box 4. An amount in parentheses is a negative amount. Enter this amount on line A of IRS Notice 703 to see if any of your Social Security benefits are taxable.

Box 6–"Voluntary Federal Income Tax Withheld"– shows the total amount of benefits voluntarily withheld and paid for Federal income tax. Include this amount on your income tax return as tax withheld.

If You Have Any Questions

If you have any questions about the amounts on this form, call or visit any Social Security office. Please have this form with you. Please use the claim number shown in **Box 8** if you contact SSA. If you have questions about how to figure the taxable part of your Social Security benefits after you complete Notice 703, call IRS on the IRS toll-free number for your area.

Facts About Computer Matching Programs

Congress passed a law (PL 100-503) in 1988 that says you have a right to know that we may use information you give us when we match records by computer. Below, we tell you about computer matching and how it may affect you.

What Are Computer Matching Programs?

Computer matching programs compare Social Security and/or Medicare records with those of other Federal, State, or local government agencies. Many agencies may use matching programs to find or prove that a person qualifies for benefits paid by the Federal Government.

How Do Computer Matching Programs Affect You?

On forms that you fill out for us you give us information about yourself. Sometimes, we check the information you, and others, give us. We use computer matching to do the checking. The law allows us to check this way even if you do not agree to it. We may also share information about you with other government agencies that pay benefits. They will use this information in their computer matching programs.

If You Want More Facts

If you want to learn more about computer matching or how we use information about you, please contact any Social Security office.

EXHIBIT 1

Notice 703
(Rev. September 1999)

Department of the Treasury
Internal Revenue Service

Read This To See If Your Benefits May Be Taxable

If your Social Security and/or SSI (Supplemental Security Income) benefits were your only source of income for 1999, you probably will not have to file a Federal income tax return.

Fill in lines A through E below to see if you may have to include part of your Social Security benefits on your 1999 Federal income tax return.

Part of your Social Security benefits may be taxable if, for 1999, you were:

1. Single, and line E below is more than $25,000.

2. Married, and

- You would file jointly, and line E below is more than $32,000; or
- You would file separately, and line E below is more than zero (more than $25,000 if you lived apart from your spouse for all of 1999).

Note: *If you plan to file a joint income tax return and your spouse also received a Form(s) SSA-1099, add your spouse's amounts to yours on lines A, C, and D below. Even if your spouse did not receive a Form(s) SSA-1099, include his or her income on lines C and D.*

A Enter the amount from box 5 of all your Forms SSA-1099. If both you and your spouse received a Form SSA-1099, see the **Note** above . . . . . **A** _____
If line A is zero or less, stop here; none of your benefits are taxable this year.

B Enter one-half of the amount on line A. . . . . **B** _____

C Enter the total of any taxable income such as taxable pensions, wages, interest, and dividends . . . . . **C** _____

D Enter any tax-exempt interest such as interest on municipal bonds. . . . . **D** _____

E Add lines B, C, and D, and enter the total here. **Then, read the information below.** . **E** _____

If your figures show that part of your benefits may be taxable, see Social Security Benefits in your Federal income tax return instructions. If they do not, none of your benefits are taxable this year unless you exclude income from sources outside the United States, interest income from series I or series EE U.S. savings bonds issued after 1989, or employer-provided adoption benefits. For more details, get IRS Pub. 915 or contact the IRS as explained below.

Note: *If your figures show that part of your benefits may be taxable and you received benefits in 1999 that were for a prior year, see Pub. 915 for rules on a special election you can make that may reduce the amount of your taxable benefits.*

Get More Information From the IRS

If you still have questions about whether your Social Security benefits are taxable, see the 1999 Federal income tax return instructions for ways to get help from the IRS. If you do not have the instructions, you can get your questions answered by:

- Calling the IRS at 1-800-829-1040.
- Sending written tax questions to your IRS District Director. To get the address, call 1-800-829-1040.
- E-mailing the IRS at www.irs.ustreas.gov.
- Using TTY/TDD equipment. Call 1-800-829-4059.

DO NOT RETURN THIS NOTICE TO THE SSA OR THE IRS

Form SSA-1099-SM (1-2000)

See the Social Security Benefit Statement on the Reverse

EXHIBIT 1

Your New Benefit Amount

NAME: SARA J BURNS

SOCIAL SECURITY NUMBER: 354-56-0231 A

Your Social Security benefits will increase by 2.4 percent for the year 2000, based on a rise in the cost of living. You can use this letter when you need proof of your benefit amount to receive food stamps, rent subsidies, energy assistance, bank loans or other business.

How Much Will I Get And When?

- Your new monthly amount (before deductions) is $801.50.
- The amount we're deducting for Medicare is $45.50.
  (If you did not have Medicare as of Nov. 19, 1999, or if someone else pays your premium, we show $0.00.)
- After taking any other deductions, we will deposit $746.00
- into your bank account on Jan. 3, 2000.

If you disagree with any of these amounts, you should write to us within 60 days from the date you receive this letter.

What If I Work Or Want To Return To Work?

If you receive disability benefits or Supplemental Security Income payments, you must report all earnings. There are special rules that help disabled and blind people return to work. Contact us for the free booklet, *Working While Disabled—How We Can Help* (Publication No. 05-10095).

Medicare Information

The Health Care Financing Administration recently sent the *Medicare & You 2000* handbook to all beneficiaries. The handbook contains the latest information on coverage, deductibles and health care options that may be available in your area.

If you have Medicare and limited income and assets, your state may help you pay for all or some of your Medicare expenses. You may qualify if your monthly income is no more than $947 for an individual or $1,265 for a couple (higher in Alaska and Hawaii), and you have assets of no more than $4,000 for an individual or $6,000 for a couple. Even if your income is slightly higher, you may get help in paying a small part of your medical insurance (Part B) premium. Please contact your state or local Medicaid, social services or welfare office for more information.

A Rule About Stepchildren

If a stepchild receives benefits on your record and you and the stepchild's parent divorce, you must tell us. Why? Because we must stop the stepchild's benefits the month after the divorce becomes final.

Y2K Okay

Social Security and Medicare are ready for the year 2000 (Y2K). All of our computer systems have been updated so you will receive your payments from Social Security on time, as usual.

How Do I Contact You?

You can call us at 1-800-772-1213. We can answer questions by phone from 7 a.m. until 7 p.m. on business days. If you are deaf or hard of hearing, you may call our TTY number, 1-800-325-0778. You also can reach us on the Internet at *www.ssa.gov* or visit your local office.

SUITE 1265
880 FRONT STREET
SAN DIEGO CA

If you have questions about Medicare, you can call a new toll-free number—1-800-MEDICAR(E) or 1-800-633-4227. If you are deaf or hard of hearing, you can use the Medicare TTY number, 1-877-486-2048. Also, Medicare information is available on the Internet at *www.medicare.gov.*

Kenneth S. Apfel
Commissioner of Social Security

EXHIBIT 2

8842277

UNDERSTANDING CHRONIC HEPATITIS C

SUPPORT GROUP MEETINGS

THE AMERICAN LIVER FOUNDATION'S SUPPORT GROUP MEETS AT 6:00 P.M. THE FIRST WEDNESDAY OF EVERY MONTH IN THE AMPHITHEATER AT THE GREEN HOSPITAL OF SCRIPPS CLINIC. PATIENTS WITH LIVER DISEASE, THEIR FAMILY MEMBERS AND CLOSE FRIENDS ARE INVITED TO ATTEND.

PARTICIPANTS LISTEN TO GUEST SPEAKERS AND SHARE NEWS OF THEIR PROGRESS WITH OTHER MEMBERS. EACH MONTH APPROXIMATELY 80 PEOPLE ATTEND THE MEETINGS TO OFFER SUPPORT TO EACH OTHER AND HEAR MEDICAL UPDATES FROM SPEAKERS INCLUDING SCRIPPS CLINIC'S LIVER DISEASE CENTER PHYSICIANS.

FOR ADDITIONAL INFORMATION, CALL THE SAN DIEGO CHAPTER OF THE AMERICAN LIVER FOUNDATION, (619) 291-5483.

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Medical Director, Liver Transplantation
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Lisa Nyberg, M.D.
Associate Director, Liver Transplantation
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Direct Line: (858) 554-8042
FAX Line: (858) 554-8065

EXHIBIT 3

shop transforming food into many chemical parts for use in other parts of the body. Some medicines are also changed by the liver. Your liver is also a warehouse for the body. It stores sugar and vitamins so your body can use them when they're needed. In addition, your liver is a filtering station; it takes some waste and poisons out of your bloodstream.

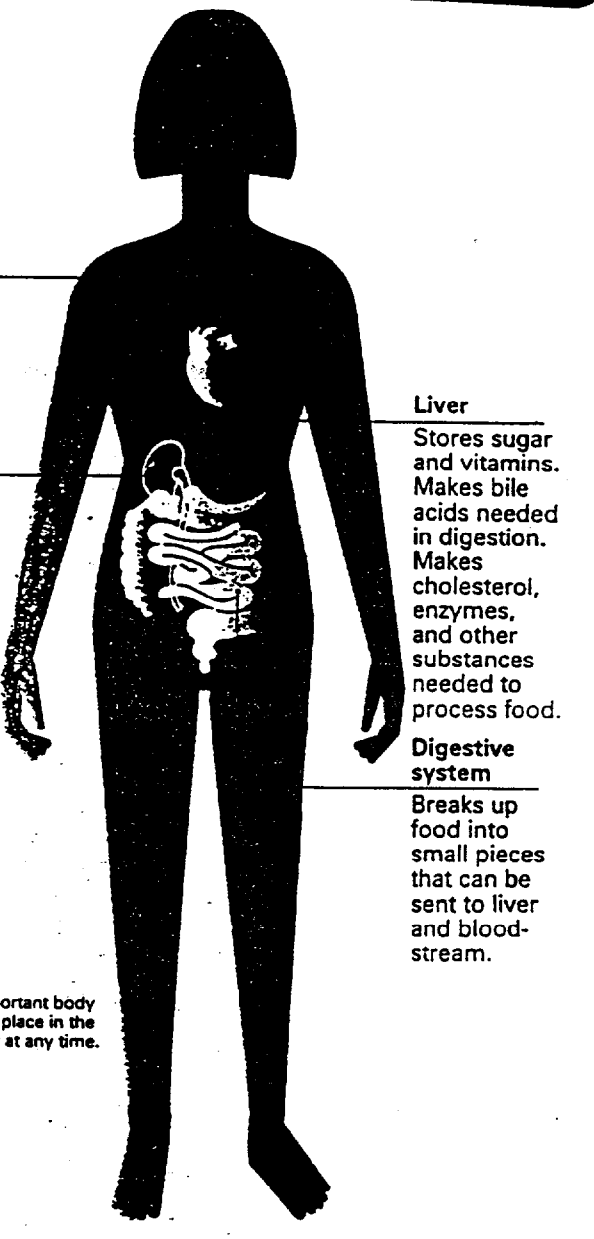
In with the good

The food we eat travels down the throat into the stomach and then on to the intestines. These organs break up the food into small pieces that can be absorbed into the bloodstream. However, that's not the last stop in preparing the food for use by the body. About 90% of these small pieces go straight from the intestines to the liver. The liver then sends this nourishment into the bloodstream so that it can be distributed to the cells that need it.

As we said earlier, your liver also stores energy. Carbohydrates, for example, are sugars that your body uses to get quick energy. Your liver stores some of these sugars and releases them between meals whenever your cells need nourishment. This way, the liver makes it easy for you to keep going all day without eating each time you need more energy.

Finally, your liver helps you digest fat and important vitamins stored in fat. Your small intestine cannot handle fat on its own, so your liver makes special substances called bile acids that break fat into pieces, almost the same way that dish detergent cuts through grease.

Some functions of the liver* and other major organs



* Thousands of important body processes can take place in the liver at any time.

cells need different kinds of proteins to do different jobs (there are millions of proteins, and they can have very different effects in the body). Your liver takes these different proteins and reshapes them, either by cutting them into smaller pieces or assembling them into larger proteins so that they are just right for use by a particular part of the body. Your liver makes or breaks down thousands of different proteins every day. Here are some of them:

- ***Fibrinogen, prothrombin,*** **and *Factors V, VII, IX,* and *X*. Proteins that are necessary for blood to clot, so that you don't bleed to death from a small cut.**
- ***Bilirubin*** **is a yellow substance that builds up in your blood as red blood cells age and break down. Your liver is responsible for breaking down bilirubin, and when your liver isn't functioning properly, you may get too much bilirubin in your system and become jaundiced, which means you have a yellowish color to your eyes and skin.**
- ***Albumin*** **is another important component of blood. It carries other substances around the body and helps prevent swelling.**
- ***Cholesterol*****, which we often think of as a nuisance, is, however, important. Cholesterol is a key component of the membrane, or outer coat, of your cells. The right amount of cholesterol is necessary for cells to function properly. It is also a building block for sex hormones and vitamins.**
- ***Enzymes*** **are involved in the chemical reactions in the body. Some of these break down molecules the body can no longer use, while others react with other proteins to keep cells healthy.**

The liver transforms medicines

Just like the food you eat, any medicine you take to improve your health also passes through your liver. The liver transforms some medicines into a form that your body can handle. For instance, any time you take aspirin, acetaminophen, or cold medicine, the liver changes these medicines, thereby helping them work in your body. Without your liver, these medicines won't work properly. So how well your liver is working will affect how much and how often you need to take a particular medicine.

Your liver is a warehouse for the body. It stores sugars and some vitamins so your body can call for them when they're needed.

What happens when my liver is injured?

Most organs get their supply of blood directly from the heart. However, because the liver has such an important role in preparing nutrition for the body, it gets its blood supply from both the heart and the digestive tract directly through a large blood vessel called the portal vein. This blood flows to millions of liver cells, called hepatocytes, which are organized into units called lobules. Each of these lobules is dedicated to carrying out the important body functions we've just discussed.

Sometimes, however, certain

have viral hepatitis, avoid alcohol completely, and closely follow your doctor's medical instructions about drugs and diet. (See Chapter 8 for more information about proper eating habits.)

Liver cancer

As we discussed earlier, when viruses like hepatitis B and C infect cells, they alter parts of the cells, including the cells' DNA. The damage to the liver cell results from the direct effects of the virus and from the immune system's response to the infection. It is the damage to the liver cells that leads to the scarring.

There's increasing reason to believe that this DNA alteration may have an important impact. It appears that while liver cells harbor virus, they go through changes that make it more likely for them to become cancerous. Patients chronically infected with hepatitis B or hepatitis C are at increased risk of hepatocellular carcinoma, a potentially deadly liver tumor. Without proper treatment about 20% of patients with cirrhosis go on to develop liver cancer.

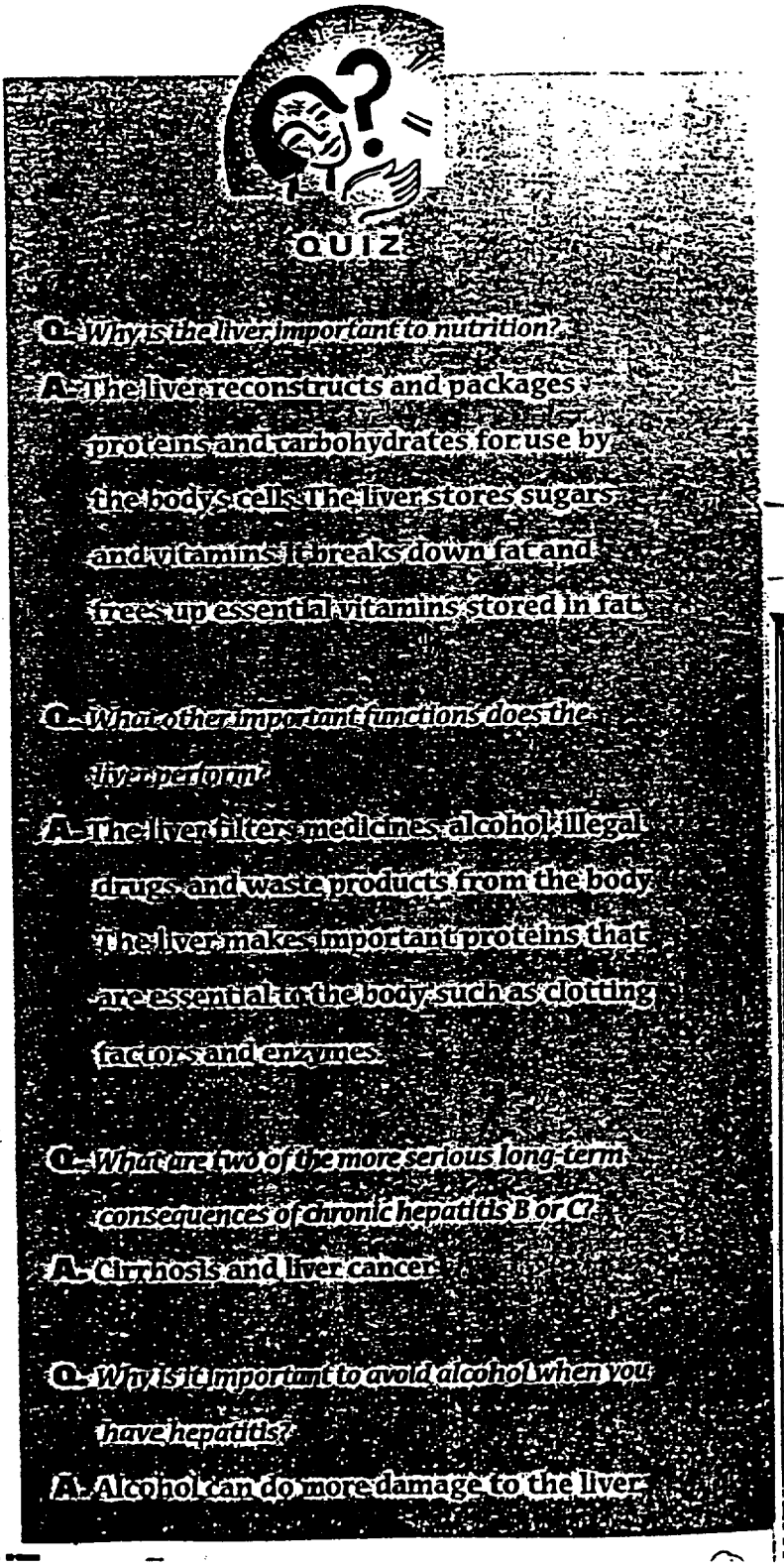
The symptoms of liver cancer are often similar to those of cirrhosis, and are listed below:

- **Jaundice**
- **Fatigue and drowsiness**
- **Weight loss**

Patients with liver cancer may find that they sometimes have severe abdominal pain. Liver cancer may also spread through the bloodstream, causing cancer in other tissues throughout the body.

If the cancer is small, it is often treated surgically. Because the liver can regrow, it's sometimes possible to remove a great deal of liver tissue without long-term ill effects. However, if the liver has been scarred and developed cirrhosis due to hepatitis C, surgery as a cancer treatment option may not be possible.

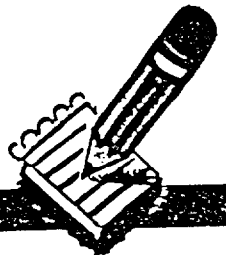
Liver cancer is frequently extensive by the time it is discovered, and cancers may recur after surgery.



ow Do the Hepatitis B and C Viruses Work?

Hepatitis is a disease of the liver that is caused by one of the tiniest types of "bugs," or microorganisms, that can infect humans: a virus. The most common symptom of hepatitis is tiredness, or fatigue. There are several different types of hepatitis, each caused by a different hepatitis virus. In each case, the virus, once inside the body, begins to live in the liver cells and then takes them over.

In this chapter, you'll learn more about viruses, particularly hepatitis B and C, and what they do in your body. This should help to explain the symptoms you feel, how these diseases are treated, and why you need to take certain steps to improve your health, such as avoiding alcohol.



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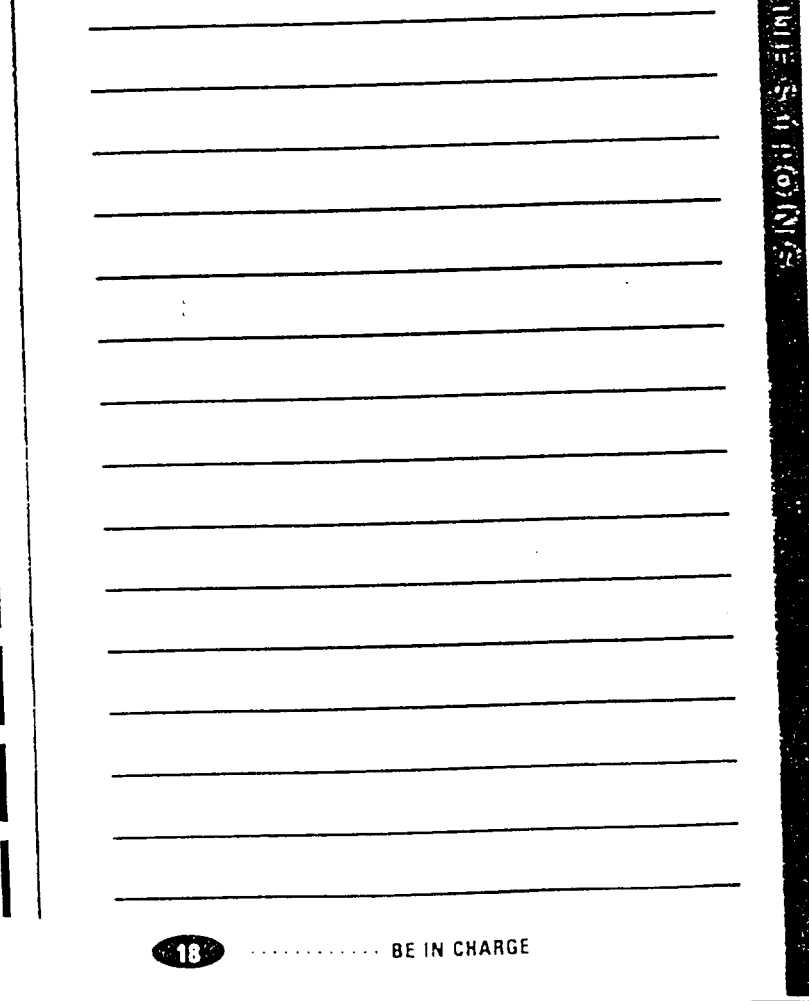


What is a virus?

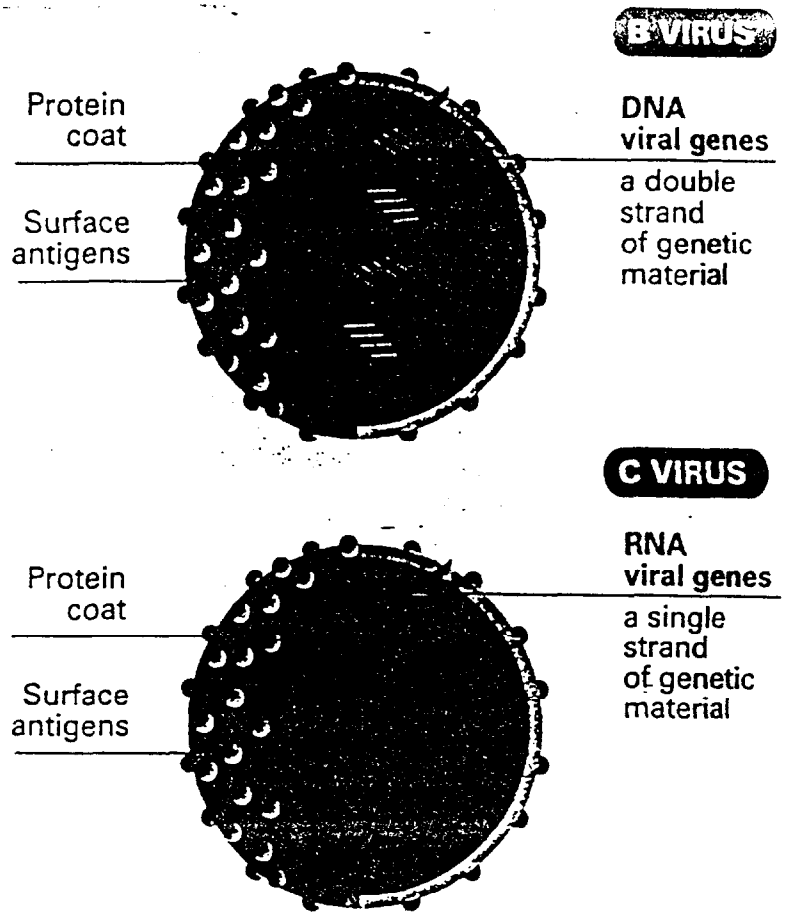
A virus is much simpler and much smaller than a human cell. It is, in fact, just made up of a compact string of genes (genes carry the coded information telling our cells what to do) in a coat of protein. Viruses carry only the tools they need to take over a cell. Among these basic tools for survival, the virus carries a blueprint so that it can make many more copies of itself once it has infected the cell. The protein coat around the virus — its capsule — also plays a critical role, as we will see.

Unlike a human cell, which contains complex biological machines to digest food, produce energy, and perform other functions, a virus exists mainly to reproduce. The virus reproduces by invading living cells. Once inside a cell it takes over the cell's normal functions and uses the cell and its machinery just to produce more virus.

Not all viruses can enter all cells. The hepatitis viruses, for example, mainly infect liver cells. When a hepatitis virus infects a liver cell, spikes on its envelope, or outer membrane, anchor to the outer surface of the liver cell. A core of viral genes is now able to pass from the envelope into the cell.

EXHIBIT 3 (5)

The hepatitis B and C viruses



ball court, while a typical human cell would be as large as a football field!

Many bacterial infections are treated with common drugs called antibiotics, and once treated effectively, they are gone forever (unless you are infected again). You may have wondered why the hepatitis virus can't be treated in the same way. Because a virus lives in the cell and uses it to reproduce more virus, most drugs that will kill the virus will harm the cell, too.

An example of a viral treatment is the drug interferon, which is used to fight hepatitis. While it has been tough to find treatments for viruses, we do have vaccines, or preventive drugs, that protect against infection by some viral diseases, such as hepatitis B, the flu, and polio.

What is the difference between an acute and a chronic illness?

Your doctor has probably told you that your hepatitis is either acute or chronic. An acute illness is one that develops quickly, has severe symptoms, and lasts for 6 months or less. A chronic illness is one that lasts longer than 6 months, and has symptoms that may disappear for a while, then recur. While some forms of hepatitis are acute, others are chronic.

Different kinds of hepatitis viruses

When hepatitis infection occurs, the liver is affected. Hepatitis simply means inflammation, or irritation,

EXHIBIT 3

changes. A mutation is a permanent change in the virus's genetic code, or makeup. Both the hepatitis B and C viruses mutate in the body, but the hepatitis C virus does this so many times that the body ends up fighting many slightly different forms (called strains) of the virus. This is why the body is so much better at fighting hepatitis B than fighting hepatitis C, and one reason why there is a vaccine for hepatitis B, but not for C. (See Chapter 12.)

Hepatitis B

Hepatitis B is caused by the hepatitis B virus. This virus has a ball-shaped capsule containing the virus's genetic material, which invades the liver, as explained above. Hepatitis B is a serious form of hepatitis that affects more than 1 million Americans, with about 140,000 more becoming infected each year.

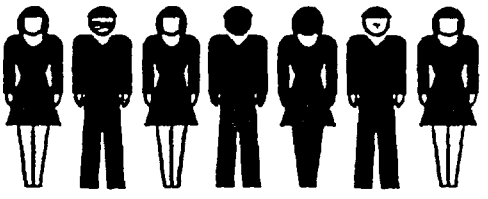
Hepatitis B virus causes the liver to become enlarged, irritated, and sometimes scarred. Hepatitis B has the ability to hide inside the body, so many people don't know that they've been infected until they are tested specifically for hepatitis B. However, some infected people will have the flu-like symptoms that you would normally expect when you have a virus: loss of appetite, upset stomach and vomiting, fever, pain in the abdomen, and so on. This is called acute hepatitis. (Remember, an acute illness is short-lasting, while a chronic disease may last a long time, recurring often.)

Other symptoms of acute hepatitis B infection are very different from having the flu. For instance, your urine may become dark, which is a sign that your liver is functioning poorly. Your liver will not be as efficient in breaking down bilirubin, and so your eyes and skin may become yellowish, or jaundiced. You may feel very tired for weeks or months. This is another sign that your liver is not removing waste from your body as quickly as it should. Finally, an enlarged liver may cause a strange feeling in the right side of the abdomen that is described by many as a heavy and dragging sensation. Many people with hepatitis B have some symptoms; it is important to know, however, that some people will have no noticeable symptoms at all. (See Chapter 7 for a discussion of symptoms and how to deal with them.)

Most adults can fight off a hepatitis B infection without treatment. But a small percentage of people go on to become carriers (having few or no symptoms but able to infect other people) and a few more become chronically infected; that is, their infection stays active for more than 6

Hepatitis C

Number of new cases in the United States per year: **150,000**



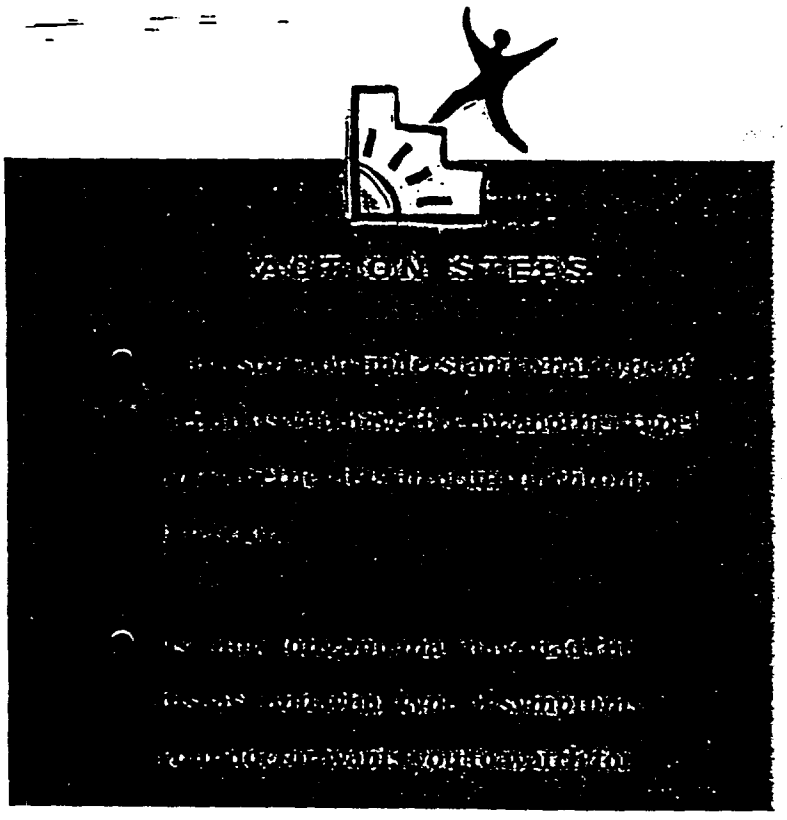
Source: Schering Oncology/Biotech, National Institute of Allergy and Infectious Diseases, April 1997.

EXHIBIT 3

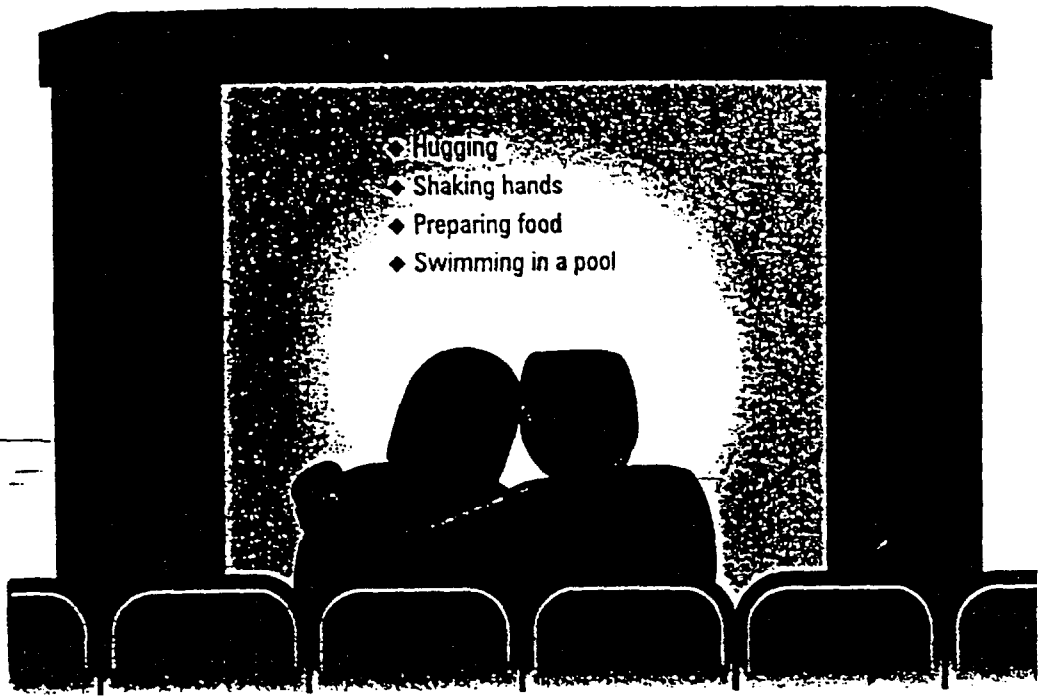
there is no way of knowing how each person's disease will progress.

About 85% of patients with hepatitis C virus infection go on to suffer from chronic hepatitis. In the meantime, just like patients with hepatitis B, you should avoid alcohol because of the additional damage it can do to your liver (and remember, alcohol and acetaminophen [an ingredient in some over-the-counter pain relievers, and many drug combinations used for colds] taken together can cause a condition called fulminant hepatitis, which can lead to fatal liver failure. Clearly, you should never combine these two substances, and talk to your doctor about any medications you take).

All of this information about the hepatitis viruses can help you better understand how hepatitis is spread, which is the topic we will discuss in Chapter 4. ▼



Some safe activities for people with hepatitis B or C



providers that you have hepatitis.

You can get hepatitis B or C if you share any kind of needles — those used for tattooing, body piercing, acupuncture, shots for health reasons, or illegal drugs. Sharing needles for illegal drug use is now one of the most common means of spreading both hepatitis B and hepatitis C. Straws for inhaling cocaine appear to be another major means of infection — small amounts of blood from inside the nose stick to the straw, which is then passed to the next person. This is now a common way that hepatitis is spread.

I didn't know that! →

Sex and transmission from mother-to-baby are two other ways that hepatitis B and C can be spread, but there are important differences between the two viruses in these cases, as we will discuss in the next section.

How you acquired hepatitis B or hepatitis C, whether it was through a transfusion, drug use, or some factor you can't even remember, does not make a difference in how either disease will affect you. But learning about how these diseases are spread can help you protect your family and friends, and protect yourself against other infections.

Having hepatitis does not protect you against other infections, and because there are at least six hepatitis viruses (hepatitis A, B, C, D, E, and G) it is possible to become infected with different types of hepatitis at different times, or even at the same time.

Learning about how these diseases are spread can help you protect your family and friends, and protect yourself against other infections.

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and pregnant, there seems to be a greater risk that your b[illegible] can catch hepatitis C from you.

Breastfeeding is usually safe for mothers with hepatitis C. Mothers with hepatitis B, however, may be able to pass the virus on through breastfeeding. Every pregnant woman with hepatitis should talk to her doctor about how best to protect her baby from this virus.

Quick protection against hepatitis B

If someone is exposed to hepatitis B, he or she should call their doctor immediately. Anyone who is exposed to this virus must receive an injection of HBIG, which provides temporary help in protecting the person from the virus, followed by the series of 3 vaccinations against hepatitis B.

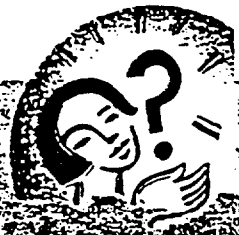
For the best protective effect, the HBIG should be given within 24 hours after coming into contact with the virus. The vaccine involves 2 injections given a month apart, followed by a third injection 6 months after the first one. The hepatitis B vaccine is useful only for people who do not already have a chronic hepatitis B infection.

Most people find out they have hepatitis C a long time after they were exposed to the virus. There is no vaccine or immune globulin currently available for hepatitis C.

Protecting others

It's natural to be worried about passing the virus on to family, friends, and coworkers. Here are some things you can do to protect other people:

- Protect others by covering open wounds and by not sharing



QUIZ

Q. *Can needles that have been used on or by other people carry hepatitis viruses B and C?*

A. Yes. Needle sharing for illegal drug use is now one of the most common ways of spreading both these diseases. And both hepatitis B and hepatitis C can also be spread through contaminated needles used in tattooing, body piercing, acupuncture, and for injections of drugs used for health purposes.

Q. *Can hepatitis B and hepatitis C be spread through the sharing of personal care items?*

A. Yes. Any object such as a razor, an earring, or a toothbrush may carry enough virus-laden blood to infect another person.

Q. *Which is more contagious, hepatitis B or C?*

A. Hepatitis B is more contagious than hepatitis C.

Q. *If you are pregnant and you have hepatitis B, what does your baby need right after birth?*

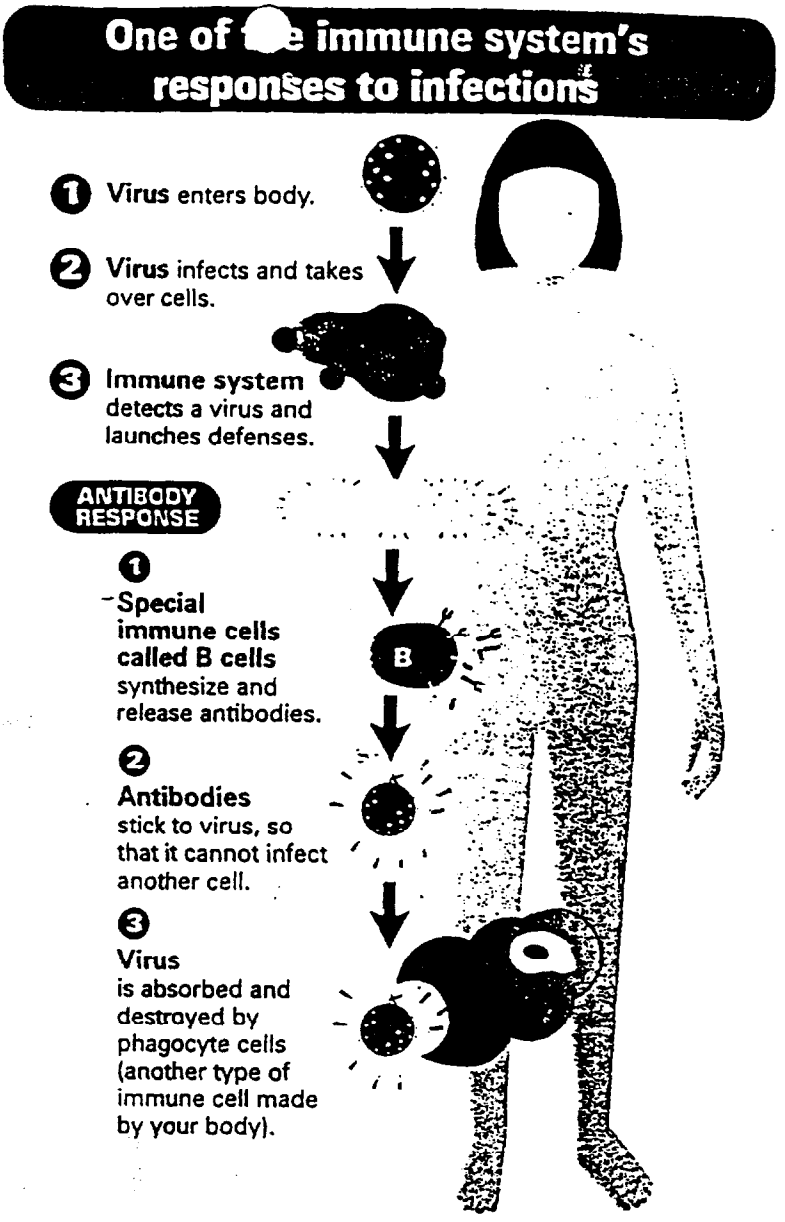
A. An injection of HBIG (a special type of immune globulin), and the first in a series of three hepatitis B vaccines.

damage to the body's cells to trigger the immune system that symptoms occur — usually about 4 to 6 weeks after someone is infected.

Even before an infected person starts feeling symptoms, he or she is infectious to others. In fact, people with hepatitis B or hepatitis C may be able to infect other people as soon as 2 weeks after they themselves have become infected, whether or not they have symptoms.

How doctors test for hepatitis

In many cases, particularly with hepatitis C, the infected person will have no symptoms. Many of these people find out that they are infected with hepatitis years later, while having a routine physical exam, or perhaps if their blood is tested while buying life insurance, obtaining a marriage certificate, undergoing fertility



■ Antibodies, B cells, and phagocytes are all immune cells that your body uses to fight infections.

Dialogue Box: START TALKING TO YOUR DOCTOR

Patient: When we last met you told me I had hepatitis. I've had some time to think about this, and I have a lot of questions. First of all, is it clear that I have an active infection, or was this a past infection that is over now?

Doctor: The test showed that you have active hepatitis C in your body right now.

Patient: What tests have you done so far? What do they tell you about how serious my infection is, and how my liver is working?

Doctor: We have just started looking at that, and I won't know for a while.

Patient: Can you please review for me which tests you plan to do, and what each one means?

(Doctor and patient review tests and their meanings together.)

Patient: Thank you. How will I find out the results of these tests? Will we discuss the results and my options?

Doctor: You need to make an appointment to come back and get the test results. We can review their meanings then.

Patient: Good, I need as much information as I can get about my condition, and this conversation has helped me a lot. I appreciate your taking the time to explain this to me.

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antibody-IgM (anti-HBc-IgM), the hepatitis B core antibody-IgG (anti-HBc-IgG), the hepatitis B e antibody test (anti-HBeAg), and the HBV-DNA test, that will help determine if the infection is old or new, and whether you are still successfully fighting it off, or if you need treatment and are still infectious to other people. (See Chapter 4 for a discussion of how the virus is spread.)

For hepatitis C, your blood is tested for antibodies to the hepatitis C virus using the enzyme-linked immunosorbent assay (ELISA). (Remember, the antibodies your body produces against hepatitis B are much better at killing the virus than those directed at hepatitis C. So finding antibodies to hepatitis B in your blood might mean your body is still fighting, or has killed, the virus. But finding antibodies to hepatitis C probably means you are still infected.)

Good to know!

Once your body has encountered a virus, and made antibodies to it, it keeps the antibodies around just in case the virus comes back, sometimes for decades or longer. For this reason, finding antibodies doesn't answer all of your doctor's questions about your hepatitis C infection.

To find out more, your doctor may give you the recombinant immunoblot assay test (RIBA), which is another way of measuring the presence of various antibodies to hepatitis C in the blood, or you may be given a polymerase chain reaction (PCR) test that tells your doctor how much virus is in your blood. (The PCR test for HCV is called the HCV-RNA test.) These tests are often used only to confirm your diagnosis, or to follow up on your progress.

Another common test used is the liver biopsy, in which a small piece of liver is removed (too tiny to examined. Many physicians do a liver biopsy whenever a patient has a high ALT, suggesting the liver is inflamed, to help them confirm what exactly is causing this problem and how serious it is. Others think

QUIZ

Q: How does the body fight infection?

A: One of the main ways the body fights infection is by producing antibodies that attack the invader.

Q: How soon after infection can a person infect someone else?

A: A person infected with hepatitis B or C may become infectious to others as soon as 2 weeks after being infected themselves.

Q: What are the most common tests for hepatitis?

A: The hepatitis B surface antigen test (HBsAg) tells you if you have hepatitis B virus in your blood. An antibody test for hepatitis C tells you that you have been exposed to hepatitis C and it is very likely the virus is still present. The alanine aminotransferase test (ALT) simply tells you if it is possible your liver is inflamed. The polymerase chain reaction (PCR) test (HBV-DNA or HCV-RNA) may determine how much virus is in your blood.

How Is Hepatitis Treated?

Treating your hepatitis quickly is the most important thing you can do. Unless your body has fought off the infection by itself, treatment may be your only hope of controlling chronic hepatitis B or C. Sometimes the treatment takes a long time, and it does not help everyone, but because this disease can get worse over time, it is very important to get proper treatment and follow-up.

In this chapter, you'll learn important details about the therapy, such as how long it takes, who benefits the most, and the best ways to deal with side effects. Remember to write down any questions you have for your doctor about the therapy.

What is interferon?

Interferon is a drug approved by the U.S. Food and Drug Administration (FDA) for treating chronic hepatitis B or C. [Note: Interferon is the general name of the drug. There are different forms of interferon, just like there are different forms of pain relievers like aspirin or ibuprofen. INTRON® A (Interferon alfa-2b, recombinant) Injection is the first and only interferon cleared by the FDA for treating chronic hepatitis B. It was also cleared by the FDA in 1991 for chronic hepatitis C.]

Interferon can completely eliminate chronic hepatitis B infections in some people. In people with chronic hepatitis B or C it may slow the disease by reducing the amount of virus in their body and slowing the damage to their liver. It is very important that you find out immediately if you should get treatment: the timing of your treatment can greatly affect your chances of benefiting from interferon.

Not everyone benefits from interferon therapy. You need to talk to your doctor about this therapy and its associated side effects, which are discussed later in this chapter. If the hepatitis B or C virus has already seriously damaged your liver, drug treatment may be out of the question; it might make you sicker without helping to cure the disease.

Finally, if you have chronic hepatitis but no sign of liver damage, it may not be worth it to take interferon. Your doctor will have to help you make a choice about treatment.

If your doctor does not recommend that you try interferon therapy, find out why he or she thinks treatment wouldn't work for you. Ask whether treatment may be possible, or even necessary, in the future if your condition changes.

To improve your chances of controlling your chronic hepatitis, you need to find out as much as you can about interferon, your particular case of hepatitis — how your liver is working, what type of virus you have, whether the infection is new or old — and what you will need to do to make sure therapy works.

How interferon works

One way the drug interferon works against chronic hepatitis is by protecting your healthy, uninfected

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ple. Others will have chronic hepa B for the rest of their lives, which means that the virus will continue to attack liver cells.

One way that interferon works is by stimulating the immune system's attack on the infected liver cells. As a result, the patient may actually have a period during treatment in which his or her symptoms are worse than before. Remember, the virus makes your immune system attack infected liver cells. This proces is called a flare. It may be a good n because it occurs more often in responders than non-responders in patients being treated for chronic hepatitis B.

Before treating any patient for hepatitis B, a doctor will check to determine that there is virus currently present in the patient's blood and that the patient's liver is being damaged. As we noted earlier, if the patient is too sick, the therapy may do more harm than good. The level of virus in your blood before treatment, as shown by a hepatitis B virus DNA test (HBV DNA), may help predict whether or not you are likely to be helped by interferon. People with less virus seem to get more benefit from interferon than those with higher levels of virus.

NOTES & QUESTIONS

What to expect from treatment

The treatment for chronic hepatitis B involves taking injections of INTRON® A (Interferon alfa-2b, recombinant) Injection for 4 months.

Several things, particularly how long you have been infected with the virus, will make a big difference in whether or not it is likely you will be cured. But there is no easy way to tell which patients will get better after taking interferon. About half of all patients with chronic hepatitis B who are treated with interferon will have some benefit from the treatment — there will be less virus in their blood, their liver damage may have slowed, and their symptoms will improve. In clinical studies, 45% of patients who are treated for chronic hepatitis B with INTRON® A will have no evidence of the hepatitis virus in their blood over time.

While you are being treated, your

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So it is very important that you stick to your treatment for as long as it takes to see if you are improving.

— because the drug will not have completely cleared the virus from the body.

Even if the virus is controlled, it can take time for your liver to recover from the infection. Despite the absence of virus, the liver needs time to grow healthy new cells to replace those that were damaged or destroyed by the infection.

Treating hepatitis C

As we noted in Chapter 5, the antibodies your body produces to defend against hepatitis B work much better than those directed at hepatitis C. As a result, your body more often needs help beating chronic hepatitis C.

Again, your doctor will try to see just how much damage your liver has had before starting your therapy. The drug is usually given 3 times a week, and treatment often lasts much longer for chronic hepatitis C than for chronic hepatitis B; it may take anywhere from 12 months to 2 years for your treatment to be completed. During treatment, your doctor will carefully follow your ALT level and HCV-RNA levels and do other tests to see if your liver is getting better through treatment.

Studies have suggested that longer treatment leads to better results. These benefits may include periods of remission and a lower risk of developing cirrhosis and/or liver cancer. So it is very important that you stick to your treatment for as long as it takes to see if you are improving. Often your doctor can tell after about 3 months of treatment whether or not interferon is helping you. At that point, he or she may recommend that you stop the drug if it doesn't seem to be working, or your doctor may change your treatment.

Follow-up with your doctor, even if you seem to be rid of the virus, is very important. At the end of therapy, your doctor may again test for the presence of the virus and may measure its level in your blood using the HCV-RNA test. Even if you have no sign of the virus in your body at the end of treatment, there is a greater than 70% chance that you will suffer a relapse, or return of your infection. If this happens, you may need another round of treatment. Now, many patients who have a relapse have a good chance of responding to combination therapy. (See page 45 for additional information.)

As with chronic hepatitis B, it seems that how much hepatitis C virus you have in your blood may affect whether or not interferon will help you. It also seems that the amount of virus, and the related damage to your liver, increases with time. This makes it especially important for you to get treatment as soon as possible.

Coping with side effects

Almost everyone who uses interferon notices side effects, some of which are unpleasant. But you should not let that discourage you from using it. Some of the side effects of interferon are similar to the symptoms of hepatitis, so you may use some of the same approaches (discussed in Chapter 7) to handle these problems whenever they arise. There are also ways to lessen the unpleasant effects that

Go to know ←

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you'll have side effects on only 2 of your workdays. You'll need to take your injections at the same time and on the same day each week.

Drinking plenty of fluids (without caffeine or alcohol) may help relieve the side effects. It is especially important to drink water or clear fruit juices (apple, cranberry, or grape) right before and right after receiving the injection.

Some people take over-the-counter pain relievers 1 hour before their injection to help relieve side effects. Others have found that 1 tablet of the pain relievers 2 or 3 hours after the injection works better in relieving the side effects. It is important that you talk to your doctor before taking any over-the-counter or prescription medication for side effects. (Remember, alcohol and acetaminophen [an ingredient in some over-the-counter pain relievers, and many drug combinations used for colds] taken together can cause a condition called fulminant hepatitis, which can lead to fatal liver failure. Clearly, you should never combine these two substances, and talk to your doctor about any medications you take.)

Some medication can have bad effects when taken during interferon therapy. You must tell your doctor about any other medications, including vitamins or any herbal remedies you take regularly for your health. Some medications don't work as well if they are taken with another drug, or can cause a bad reaction, so it is important that your doctor knows about any other medicines you are using while you are getting interferon.

You must tell your doctor about any other medications, including vitamins or any herbal remedies you take regularly for your health.

You can try relieving headaches with massage, heat applied to the back of the neck, or just resting. Fever can sometimes be reduced by sponging yourself with lukewarm water (don't use cold or hot water). Eating can be a problem if you are nauseous or just have no appetite. You may want to eat several small meals throughout the day, or have some healthy snacks on hand for nibbling when you feel up to it. Food is very important to keep yourself well nourished during treatment. (See Chapter 8 for a discussion of proper eating habits.)

Your emotional well-being is also important to getting you through this, so be aware of the symptoms of depression and other troubling feelings. Infrequent reports of suicidal behavior (ideation, attempts, and completed suicides) have been associated with interferon treatment. (See Chapter 9.)

Good oral hygiene, such as using mouthwash and brushing your teeth several times a day, may help get rid of the metallic taste. There isn't much you can do about hair thinning, but your hair loss will be mild and it will stop falling out and grow back once the interferon therapy is completed. In the meantime, you might want to get a hairstyle that makes your hair look more full, use hair extensions, or experiment with caps and scarves.

More serious side effects can also occur, so report any changes in

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If your doctor prescribes combination therapy as treatment for chronic hepatitis C, you will need to take REBETOL® (Ribavirin, USP) Capsules twice a day, in the morning and in the evening, and you will also take injections of INTRON® A (Interferon alfa-2b, recombinant) Injection three times a week. The amount of REBETOL® your doctor prescribes will be based on your body weight. Your doctor will monitor how you are feeling and how you are responding to treatment. The approved length of treatment for REBETRON Combination Therapy, a treatment combining REBETOL Capsules and INTRON® A Injection, is 6 months. You should follow your doctor's recommendation on the appropriate use of this therapy. The FDA has approved REBETRON Combination Therapy only for patients who have relapsed following treatment with interferon alone.

What to expect from REBETRON Combination Therapy

While you are receiving REBETRON Combination Therapy, you will have several different lab tests so your doctor can monitor you for potential side effects. If HCV RNA is found in your blood, your doctor can tell that the hepatitis C virus is still present. One way your doctor can usually tell if you are responding to treatment is by testing to see if you have reduced levels of alanine aminotransferase (ALT) — an important liver enzyme described on page 34. Your ALT levels will be checked when you first start treatment, then followed to see if they are decreasing. If your test results show that your ALT levels are decreasing, then fewer liver cells are dying or being damaged. That's a good sign.

REBETRON Combination Therapy could seriously harm your unborn child. If you or your partner are pregnant, you should not receive REBETRON Combination Therapy. A woman of childbearing age must have a negative pregnancy test before starting on REBETRON Combination Therapy. She must also have a pregnancy test each month during treatment. If you or your partner become pregnant while on this therapy or during the 6 months after stopping therapy, consult your doctor immediately.

Pregnancy should not be planned while you or your partner are on REBETRON Combination Therapy or for the 6 months after therapy. Both male and female patients must use effective contraception during treatment and for the 6 months after treatment is completed. You should discuss with your doctor how you or your partner can prevent getting pregnant.

Side effects of REBETRON Combination Therapy

Since REBETRON Combination Therapy includes the use of INTRON® A, any of the side effects described on page 42 are possible. Fatigue is a common side effect, as well as flu-like symptoms (muscle aches, fever, and chills) and depression. Very infrequent reports of suicidal behavior (ideation, attempts, and completed suicides) have been associated with interferon treatment. If your side effects from REBETRON Combination Therapy are severe, your doctor may need to change your level of these drugs or stop treatment completely. You can also help yourself by trying some of the coping tips on page 42.

feel that you can continue running, find another way to exercise, even if it's a short, regular walk. And if you weren't exercising before, now is a good time to start. But start out slowly, as you should when beginning any fitness program under any circumstances. Check with your doctor before beginning any new exercise program.

Good idea! →

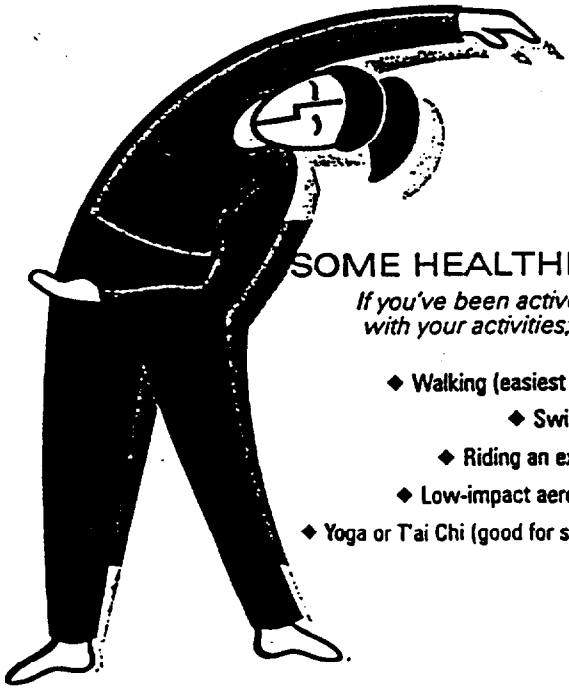
Walking may be the best option. It is free and easy to do almost anywhere, and it gives your body a good workout. Build up speed and distance slowly; the most important thing right now is just to be doing it. Other good choices are swimming, using an exercise bike, and yoga. (See chart of exercise ideas below.)

Another way of coping with fatigue is to get on a regular schedule. Rest is very important. You need to make sure you get a full night's sleep every night. A 30- to 45-minute daytime nap can help give you an energy boost.

You should let your doctor know if you are having any difficulties sleeping. If you have a stressful job, you may need to make some changes to lessen your workload. (See Chapter 11 for more about hepatitis and your job.) The same holds true for a hectic home life. Other family members may need to take over some of the responsibilities. (See Chapter 10.) Sometimes the fatigue is severe, especially with hepatitis B. If you feel very tired, let your doctor know so you can discuss the best way to cope with this.

Joint and muscle aches

You may experience joint and muscle aches and pains with hepatitis; the symptoms can seem like those of arthritis. But hepatitis does not cause arthritis and these symptoms typically go away when the virus has been cleared from your body. Over-the-counter pain relievers can help relieve the pain. However, any medication may affect your liver. Talk to your doctor about what types of pain relievers you can take, how much you can take, and for how long.



SOME HEALTHFUL ACTIVITIES

If you've been active, you can continue with your activities, if you feel up to it.

- Walking (easiest and cheapest)
- Swimming
- Riding an exercise bicycle
- Low-impact aerobics class or video
- Yoga or T'ai Chi (good for stretching and reducing stress)

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don't understand how you feel. You might feel tired all time, or that you don't have enough energy, or that no matter how much you sleep, you just don't feel like getting out of bed. By 9 AM, you feel as if you've put in an entire workday. But you can get help to cope with these feelings. (See Chapter 9.)

Other ways to relieve symptoms

Perhaps the most important thing you can do to cope with symptoms is to have a positive attitude. Replacing negative thoughts with positive ones is easier said than done, but it will make a difference in how you cope with your illness. Increasing your activity level, making yourself smile more often, and even volunteering your time to help others are all ways to start feeling better about yourself. Having a better attitude may not lessen muscle aches, but it will go a long way in helping you live with the symptoms of hepatitis.

Many people also have looked beyond traditional medical care to find relief for their symptoms. For the symptoms of stress and depression in particular, many hepatitis patients have used stress management and relaxation techniques, including the following:

- **Meditation. There are many different meditation methods, but they all work to quiet the mind and make you feel more peaceful and relaxed.**
- **Yoga. This is a slow stretching exercise that tones the body and relaxes the mind.**
- **T'ai Chi. One of the Asian martial arts that is different from judo or karate. The movements are slow and energizing, and, like yoga, it relaxes you as well.**
- **Relaxation tapes. There are a wide variety to choose from. Some are musical, others have guided meditation. Choose a tape that works for you.**
- **Journal writing. Recording your thoughts in a journal often helps, especially if you do not feel comfortable discussing certain issues with friends or family. In addition to writing about your thoughts and feelings, you can keep track of your progress and list your goals so that you can see that you're taking control.**

Some people also use alternative or natural remedies to treat their physical symptoms. Among the options you have are herbs and homeopathic medicines (which contain tiny amounts of substances that, in large amounts, cause symptoms like those of the disease they are aimed at treating), altering your diet, and taking vitamin and mineral supplements. Some people go to chiropractors (who believe that better bone alignment improves health) or naturopaths (who only use "natural" remedies, such as herbs, sunlight, and massage). Be sure you speak to your doctor before using any other therapies or beginning a stress management program; it will help your doctor to better plan your overall care. (See Chapter 6.) He or she may also have advice about what to try, whom to see, or where to get better information about the possible good or bad effects of such therapies. (See Resource List.)

Coping with other infections

Having hepatitis does not make you more likely to get other illnesses, even though you may feel like it does. It's sometimes hard to take

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healthcare provider can tell you more about your b 's particular risk and how to protect him or her.) In general, the baby does not contract the virus in the womb; rather, it is believed that the infection happens during the birth process. (See Chapter 4.)

Fortunately, there is a vaccine that can be given for hepatitis B right after birth. A vaccinated baby has very little risk of getting the virus or becoming a carrier. Therefore, the mother should try to receive interferon treatment before she gets pregnant or after she finishes nursing.

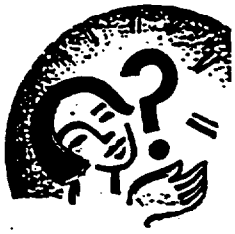
It is vital that all of your healthcare provider's staff (including those where you plan to deliver) know you have this disease. This will protect your baby, the delivery staff, and you, because your disease may mean that you will need special care.

Alcoholism

Alcohol destroys liver cells. Studies have shown that people with hepatitis C who drink three drinks a day are more likely to get cirrhosis and possibly liver cancer than those who drink less. By far the safest course of action is not to drink alcohol at all. If you are a heavy drinker, you must stop. Doctors do not know whether 1 or 2 drinks a day increases the rate of liver disease. So stopping altogether is by far the safest route. If you have a problem with alcoholism or are a heavy drinker and are unable to stop, you should speak to your doctor about a treatment center. Or you can join a support group such as Alcoholics Anonymous (AA). There are local groups in every city. (See Resource List for more information.)

Drug abuse

Using illegal dru_ can harm your overall health. If you are using intravenous drugs, you can also infect yourself with another virus, such as HIV, and you can



QUIZ

Q. *What is the most common symptom of hepatitis?*

A. **Fatigue (severe tiredness) is the most common symptom of hepatitis.**

Q. *What is a good and simple exercise?*

A. **Walking is a good exercise that can be done regularly by almost anyone.**

Q. *What potentially serious condition can cause joint pain in hepatitis patients?*

A. **A condition known as cryoglobulinemia is sometimes the cause of joint pain in hepatitis patients. You need to talk to your doctor if you think you have this condition.**

Q. *What is the most important step in dealing with symptoms?*

A. **Your attitude, and how you take control of your life through it, can make the biggest difference in how you feel, despite this disease.**

iet and Liver Disease

What you eat and drink can and does affect your liver. When you have hepatitis, eating well and avoiding alcohol are important steps in your treatment plan. Both can make a difference to your health and happiness.

When it comes to eating and drinking, you're in charge. Some food and beverage choices are smarter than others. Remember, eating well may help you feel better since it can help your body better respond to treatment and its side effects. In this chapter, we'll give you some guidelines for developing good eating habits. Proper diet can help your body heal itself and help you keep up your energy to fight off fatigue.

Unfortunately, when you feel ill, you might not feel hungry or you may have little interest in food. Eating simply may not seem as enjoyable. Being sick is stressful enough. Mealtimes should not become yet another source of stress. Your doctor or nurse may suggest you speak with a registered dietitian who can help you with your diet and select healthy foods that you may like.

Remember, eating well may help you feel better since it can help your body better respond to treatment and its side effects.

Diet and cirrhosis

If you have advanced liver disease, such as cirrhosis, weight loss may be a problem. When you aren't eating well, your body may call upon its energy stores. For example, if you are not eating enough protein-rich foods, your body may take protein from the protein that makes up your muscle. This will leave you feeling even weaker, so try to maintain your protein and calorie needs.

To quickly determine your daily protein needs in grams, divide your weight in pounds by 2. (For example, a 150-pound man will need 75 grams of protein.) To figure out your daily calorie needs, you'll need a minimum of 15 calories a day for each pound you weigh. (Again, a 150-pound man would need a minimum of 2,250 calories a day.)

Keep your salt levels below 2,000 milligrams a day. This means not shaking salt onto your food, and reading food labels carefully to determine sodium content. Limiting sodium is helpful because your body may hold onto extra fluid, and make you feel bloated. If fluid is held in the belly, the condition is called ascites; it is called edema if it is held in the legs. To cut down on salt, eat more fresh foods, most of

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Choose 5 or more servings of vegetables daily, including at least one serving of a dark leafy green or dark orange vegetable, such as:

- 1/2 cup cooked carrots or chopped vegetables
- 1 cup lettuce or spinach

Choose 2 to 3 servings equaling 5 to 7 ounces daily of meat, poultry, fish, and other protein foods, such as beans, eggs, tofu, and unsalted nuts. Any of the following is equivalent to a 1-ounce portion of meat, fish, or chicken:

- 1 egg
- 1/2 cup tofu
- 1/2 cup cooked beans
- 2 tablespoons peanut butter

Choose 2 to 3 servings of milk, cheese, or yogurt daily. Any one of the following is equivalent to one serving of a dairy product:

- 1 cup milk
- 1 cup yogurt
- 1 1/2 ounces of cheese

If you aren't having problems with fluid retention, you can determine your daily fluid needs in ounces by dividing your weight in pounds by 2. (For a 150-pound man this would be 75 ounces, or more than nine 8-ounce glasses of fluid per day.) Choose mostly water, fruit juice, seltzers, sports drinks (such as Gatorade™), or milk. Alcohol and caffeine drinks such as coffee, tea, and cola act as dehydrators, pulling water out of your system, and are not good choices. If you are having problems with fluid retention, be sure to tell your doctor or nurse. Drinking lots of fluid is especially important if you are having interferon therapy because it may help reduce side effects.

By choosing foods carefully, you may not need a vitamin or mineral

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Make the most of each mouthful. Even if you can't eat that much food, choose foods that are high in calories and protein.

If the smell of food is bothering you when you are in the hospital, ask the food service staff, a nurse, or a family member to take the cover off of your tray before they bring food into your room, or remove the cover from your tray by opening it away from you.

When you feel nauseous

This is important! →

No one wants to eat when they feel nauseous. But try not to go for long periods of time on an empty stomach. Eat small amounts of food every 2 or 3 hours and eat slowly. Don't worry about balanced meals at this point; eat what you can tolerate and make sure to replace any lost fluids. During periods of nausea, avoid citrus juices (orange, grapefruit, pineapple). The acid may bother your stomach. Instead, try apple or grape juice, ginger ale, chicken broth, weak tea, or sports drinks, and sip these drinks slowly. If morning nausea is a problem, eat some dry crackers when you first wake up. Also, get out of bed slowly. Avoid foods that have strong smells, or are spicy, greasy, or deep-fried. If your nausea continues, your doctor can prescribe medicine.

When you feel full quickly

If your liver is inflamed or enlarged it may press on your stomach and make you feel as if there's less room for food. To lessen this problem, eat smaller portions of foods at meals, and drink liquids later. Beverages taken with your meals will leave less room for food. Instead of 2 or 3 big meals a day, try 6 small meals spread out over the day. You will eat less food at a time, but you will be eating more often. Some small meal and snack ideas include:

- a bowl of oatmeal and half a banana with milk
- canned peaches and graham crackers with peanut butter
- yogurt and pretzels
- half a turkey sandwich and applesauce
- broiled chicken (skinless) and mashed potatoes
- scrambled eggs and toast with jelly
- chocolate pudding and oatmeal cookies

Make the most of each mouthful. Even if you can't eat that much food, choose foods that are high in calories and protein. To add to the nutrition of the foods you can eat, add ingredients. For example:

- Add powdered milk to regular milk, milkshakes, even casseroles, soups, eggs, mashed potatoes, hot cereal, and puddings. Use $^1/_2$ cup of powdered milk to 1 quart of regular milk.
- Spread peanut butter on breads, tortillas, waffles, pancakes, and fruit.
- Add cooked beans or hard boiled eggs to soups, casseroles, and pasta that already contain cheese or meat.

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hepatitis. (See Chapter 9 for a discussion about coping with your feelings.)

When the liver develops cirrhosis, some healthy liver cells are destroyed and replaced by scar tissue. Scarring prevents the liver from carrying out its many tasks. More liver cells are being destroyed than are being replaced. Fortunately, eating well and avoiding alcohol can still prevent additional damage to any remaining healthy liver cells.

Finally, avoid combining alcohol and acetaminophen (an ingredient in some over-the-counter pain relievers, and many drug combinations used for colds). Taken together, they can cause a condition called fulminant hepatitis, which can lead to fatal liver failure. Clearly, you should never combine these two substances, and talk to your doctor about any medications you take.

Eating right is an important way to improve your overall health. Your feelings are another key part. In Chapter 9, you'll find out about ways to keep your mind working well, too. ▼

ACTION STEPS

- **Say no to alcohol.**
- **Eat small but frequent meals and snacks.**
- **Sip plenty of fluids throughout the day — for example, water, fruit juices, seltzers, milk, and sports drinks. If you feel sick to your stomach, avoid citrus juices (orange, grapefruit, pineapple).**
- **Choose foods rich in protein and calories when you do feel like eating.**
- **If you have cirrhosis, limit your salt and maintain adequate amounts of protein and calories.**
- **Eat a variety of healthful foods.**

Many of the bad feelings that go along with having hepatitis, such as the grief and depression, the anger, fear, and the anxiety come from not knowing what to expect. You can change that.

Start by learning everything you can about the virus, from how it affects millions of people in all walks of life, to how new treatments are offering greater hope for a cure. Reading this handbook is your first step. You can also surf the Internet for information. (If you don't have a computer at home, check your local library to see if you can use one there. But remember that there are many sites with questionable information, so choose the information you use carefully, and check it with your doctor.) Find a physician who knows about the disease, such as a gastroenterologist (a specialist in diseases of the stomach, intestines, and liver) or hepatologist (a specialist in liver disease), and talk to him or her about treatment options. Get answers from people who know what they're talking about.

Recognizing grief and depression

It can be a shock to learn that you have an illness, especially one with no symptoms, no warning, and sometimes no explanation about where it came from. It's normal for you to feel sad and to miss the life you had before your diagnosis, when you didn't have to think about doctors and medication and treatment.

Feelings of emptiness, hopelessness, and sadness are common responses to the news. So are feel-

Symptoms of clinical depression

Everyone can answer "yes" to some of these questions some of the time. But if you find you're saying "yes" to more than 4 questions and the feelings aren't going away, you may be depressed. Remember, depression doesn't have to become a permanent part of life. But beating depression calls for getting the right help.

- ☐ Do you feel sad, anxious, tearful, irritable, or hopeless for most of the day, almost every day?
- ☐ Have you lost interest in eating, sex, socializing, or your favorite activities?
- ☐ Are you eating more or less than usual? Have you gained or lost weight?
- ☐ Are you sleeping more or less than usual?
- ☐ Do you feel as if you're talking or walking in slow motion? Do you fidget constantly or find yourself incapable of staying still?
- ☐ Are you always tired? Are you too weary to tackle even small chores?
- ☐ Do you feel worthless or guilty about something?
- ☐ Are you having problems thinking, concentrating, or making decisions?
- ☐ Have you been thinking more and more about death? Do you have thoughts of giving up or wanting to die?

If you think you might be depressed, talk to your doctor. He or she can refer you to a mental health professional to help you manage your depression.

SOURCE: *Caring for the Mind*, Hales and Hales, Bantam, 1996

Coping with anger

No matter how you got hepatitis, or how long you had it before you were diagnosed, it's a diagnosis that can leave you feeling angry at the world. Maybe you were always careful about your health but ended up getting sick after a blood transfusion. Maybe you discovered that your partner infected you during sex. If you suddenly learn that you've had the disease for years, you may be angry with yourself because you feel that somehow you should have known. All kinds of troubling thoughts may cross your mind.

It is important for you to get help so you can look forward. An experienced counselor or a structured, professionally run support group can help you turn your negative feelings into a positive form of strength, and help you to accept having the disease. (See Resource List for information on support groups.) You can turn your anger into strength and put it to work for you through physical activities (such as a moderate exercise program or organizing your home). Financial and legal papers are also important to organize so that you can manage your finances better and be prepared if you need documents to support your request for time off or government aid. (See Chapter 11.) These are things you can do that can have a positive effect on your life and may make you feel better.

Making a simple to-do list, where you check off items as they are done, or setting up a chart that shows the progress for "miles walked," can be good to help yourself feel positive about accomplishments and stay motivated.

Pushing fear and anxiety aside

A lot of fear has to do with not knowing: What's going to happen next? Will I be all right? What will people think of me? How will my friends treat me now?

There are fears of rejection by others: Who should I tell? What should I say? When should I break the news to the person I'm dating, who might be at risk? Will they be more supportive of me or less? How will it affect my job? (See Chapters 10 and 11 for discussions about coping with these situations.)

Even the feeling of fear itself can be frightening. But the physical effects of fear — the pounding heart, trembling, and troubled sleep — can be controlled. Sometimes, these symptoms are just the side effects of medications or drugs unrelated to your illness. However, they may also be related to some of the medications you're taking to treat your hepatitis. Remember to speak to your doctor about any symptoms that you think may be side effects of medications.

Good idea!

Anxiety is a lot like fear. It is a feeling of uneasiness or tension in response to a real or imaginary threat. The signs and symptoms are mental and physical:

An experienced counselor or a support group can help you turn your negative feelings into a positive form of strength.

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(For more resources, including how to contact the American Liver Foundation, see Resource List.) Finally, a local mental health clinic or professional in this field may sponsor such groups, but this may require a fee from you to participate.

Helping yourself

There are a number of actions you can take to get yourself into the right frame of mind. And having a good mindset, as mentioned earlier, can help you physically, as well as emotionally. Work as many of the following suggestions as you can into your daily life.

- Get enough rest — 6 to 10 hours a night.
- Eat small, well-balanced meals throughout the day.
- Try to get some form of regular exercise, following your doctor's advice.
- Have very little caffeine and no alcohol. Drink plenty of water — 4 to 8 glasses a day.
- Talk things out with a counselor, friend, priest, rabbi, or support-group peers.
- Avoid stressful situations. If there's too much for you to handle at work, ask for help. If Aunt Mary's concern is causing your stress instead of reducing it, stay away, or find a way to accept and appreciate her concern and let her help you.
- Seek out positive-minded people and activities, such as listening to music, walking, and developing hobbies.
- Find an outlet for angry feelings, such as new hobbies or activities.
- Use relaxation techniques, such as meditation and deep breathing.

Q. *What are the main ways that your body affects your mind?*

A. The physical effects of the virus can leave you feeling tired and emotionally drained. Also, side effects of medications can make you irritable or dull your thinking power.

Q. *What are the main ways that your mind affects your body?*

A. Your feelings can affect your actions, keeping you from doing what's best for you. Also, stress can weaken your body's resistance, lowering its ability to fight off the disease.

Q. *What are two ways of finding a support group?*

A. The American Liver Foundation (see Resource List) or a healthcare provider may be able to refer you to a local support group.

Q. *What else can cause the pounding heart, trembling, and troubled sleep that sometimes accompanies fear?*

A. These symptoms can be caused by, or increased by, the side effects of medications, or drugs such as caffeine, alcohol, or cocaine.

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Talking to Family and Friends About Hepatitis

Now that you have been diagnosed with hepatitis and are learning more about the virus, you may be thinking about whether you should share this information with family members and friends you trust. These are the people who know you best and care about you the most, but it may be hard for you to talk about having hepatitis, especially at first.

You may wonder how they will react: Will they think you did something wrong to get this disease, or will they just want to help you? Having friends and family who understand and provide support can make a big difference to anyone facing an illness like hepatitis. But making the decision that you trust someone enough to tell them about this problem can be tough. Once you have reached that decision, however, it's important to be able to speak openly and give them good information. This chapter will review some of the most important things about your condition that you can tell someone close to you.

NOTES & QUESTIONS

Knowledge leads to understanding

Sometimes people are most afraid of what they don't understand, and although millions of Americans have hepatitis B or hepatitis C, most people don't know much about it. So, if you tell any of the most important people in your life about your diagnosis, tell them what you know about hepatitis, and show them materials like this handbook. It will be good for them to have more information, for several reasons:

- **You may need their support and understanding, and some will be glad to give it. But people can't help you if they don't know about your condition, and if they don't know enough about hepatitis.**
- **Because hepatitis B and hepatitis C can be spread through certain types of personal contact, it will be important for the people close to you to understand how hepatitis spreads. The more they know, the safer they will be, and the more comfortable they will feel around you.**
- **There are practical ways your friends and family members can help you: by helping with chores, errands, child care, or work. Sometimes you may need this help.**

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chapter if they have questions. But here's a brief review of some of the first things you may want to tell someone about how to protect themselves against this illness.

- **If you have hepatitis C, be sure to say that it is not very contagious, but that it is important to be careful about blood and not to share anything, such as toothbrushes or razors, that could carry even a tiny amount of blood. Tell them the virus is present in semen, saliva, and vaginal fluid, but that it is rare to catch it through sex, and it is unlikely that it's spread through kissing. Rather, hepatitis C is almost always spread through blood-to-blood contact, such as through a blood transfusion, sharing needles used for injections, or sharing nose straws (used for snorting cocaine).**
- **If you have hepatitis B, say that it is a very good idea for anyone having close contact with you to get vaccinated against this disease. Mention how important it is not to share things that could have blood on them, and tell sex partners that you need to use latex condoms to protect them, because hepatitis B is more likely to be sexually transmitted.**

Because hepatitis B is more easily transmitted than hepatitis C, it is doubly important for your own sake and the sake of your loved ones that you seek treatment and make sure

Dialogue Box: TELLING A BOYFRIEND OR GIRLFRIEND YOU HAVE HEPATITIS C*

You: I need to talk to you about my visit to the doctor. I have hepatitis C.

Your Friend: What does that mean?

You: It means my liver is damaged, and I could end up with some severe symptoms, such as fatigue and pain. Or I could be fine for a long time.

Your Friend: How did you get it?

You: I'm not sure. It's very frustrating. At some point, I came into contact with some infected blood. You can get it from a needle, or from a tool for tattooing or piercing that isn't clean. It could even come from a nail file or toothbrush with just a trace of blood on it. You can get it from blood transfusions, too, or sometimes from sexual contact.

Your Friend: I'm afraid, do you think I have it, too?

You: Well, you will probably want to be tested. But there's only a slight chance that you have it too. Most of the time, people who are steady and committed sex partners don't get hepatitis C. It travels through the blood and some body fluids, like semen and vaginal fluids, but it seems that it is almost always spread by blood-to-blood contact, like when you get a blood transfusion or share needles. If you want, we can use condoms for extra protection.

Your Friend: What am I going to do? I could have a sexually transmitted disease.

You: I know it seems scary but it's actually a disease of the liver, not a sexual disease. Sex is one way it might be spread, but the main way is through blood. I have to be careful about anyone, including you, coming into direct contact with my blood. I have to be careful with razors and toothbrushes, things like that. And I'll be taking medication, trying to eat healthy and not drink, and going to the doctor regularly.

Your Friend: Should I be taking drugs too? Is there something I can take?

You: There is no vaccine for hepatitis C yet, and drugs to treat hepatitis won't do you any good unless you are already infected. But we'll make sure you're not infected and then you can help remind me to take my medicine and take care of myself. And we just have to be a little careful.

*(*Note: If you have hepatitis B, speak to your doctor about the risks of spreading this disease to loved ones, because it is more easily passed on than hepatitis C.)*

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ACTION STEPS

- **Think very carefully about who you will tell, and why. Make sure that telling them will help you, rather than cause new problems.**
- **Tell them about the diagnosis, treatment, and symptoms. Show them Chapters 5, 6, and 7 of this handbook, which cover those topics, if they want more information.**
- **Discuss the ways the disease can be spread and precautions you'll need to take. Chapter 4 discusses the spread of the disease and may be helpful to them.**
- **Discuss ways that having hepatitis B or C may affect your life in particular. What kind of problems do you see ahead, and how can your family and friends help you?**
- **Answer any questions people may have about your illness, and share other sources of information, such as this handbook and the Resource List at the back of this book.**
- **Find out how a close friend, family member, or pastor, priest, or rabbi can help you now, before you are faced with an emergency and have no one to turn to.**

medications you need on hand.

In particular, you may need help taking care of your children if your symptoms are severe.

- **Think about your child care needs, both everyday and emergency. Then decide if you can ask some nearby friends or family members if your children can stay with them if you suddenly become ill.**
- **Make sure that the emergency-contact information at the offices of your children's schools is up-to-date.**
- **Make sure that you explain your illness to your children in terms that they can understand, depending on how old they are. (See the Dialogue Box on page 77.) You should think about the same for anyone else, such as an elderly parent, whom you are taking care of now.**
- **Also, you may want to make arrangements for someone to take care of pets or other possessions, such as plants or valuables, that are important to you, if you are unable to do so for a length of time.**

If you feel you will need a lot of help, seek it out. Look into resources you may have, such as local agencies, support groups, or the members of your church, temple, or synagogue. Don't be shy about telling your pastor, priest, or rabbi about your illness. He or she can pray with you, give you advice, and help you come up with good plans for the future.

Telling someone you have hepatitis may seem tough, but picking the right people to tell and giving them good information may help you. However, you also must consider how your illness will affect your ability to support yourself. In Chapter 11, you'll get information and advice about this very important issue. ▼

hepatitis C. (See Chapter 4.)

There are some clear advantages to telling your employer; they will understand your personal situation better, and may be able to help you cope and carry on. But there could also be a bad side if your employer doesn't understand or want to help. There are federal and state laws which offer some protection. For example, the federal Americans with Disabilities Act (ADA), which is described in greater detail later in this chapter, helps protect you from being fired or forced to leave because of your condition, as long as you can find ways to continue doing your job despite your illness. This does not mean you may not be fired or experience other discrimination if you tell your employer; it just means that you have a right to sue if he or she does not obey this law.

If you do decide to speak to your employer, you need to decide who to inform. If there's a human resources or medical department, you may want to start there. If you decide to tell your boss, choose a calm time at work and ask your boss for a moment in

Dialogue Box: TELLING YOUR BOSS THAT YOU HAVE HEPATITIS

You: Do you have a minute? There's something I need to discuss with you.

Your Boss: Sure, come on in.

You: I know that this will be as much a surprise to you as it was to me. I just found out that I've got hepatitis. It's a liver disease, and it's caused by a virus. That explains why I've been feeling a bit under the weather lately.

Your Boss: You certainly haven't seemed like yourself lately. How did you get it? When will you get over it?

You: I'm not sure how I got it, but the doctor says that really isn't the important issue anyway. Getting the right medical care is the most important thing right now. There are treatments that help some people with hepatitis, and I'm checking that with my doctor, but it probably won't be going away any time soon. In the meantime, I'm trying to get more rest than usual, and I'm also making some changes in what I eat to try to build up my strength. I just wanted to let you know what's going on, because there may be times when I need time off for medical appointments, or just to rest.

Your Boss: Well, of course, I understand about that. How much time off do you think you'll need? And can you still do your job?

You: Well, for right now I don't think I need any more time than what I get for sick days. I just wanted to be sure you understood that this is something I need to take care of, and that I will be sure to take the time only when I really need it. I can still do all of the parts of my job.

Your Boss: I see. Is there anything else that I need to know?

You: Not at this point. I've talked to my doctor about this, and she feels it's OK for me to keep working for now. I feel all right most of the time, but if I'm feeling too sick to come to work, I'll give you a call.

Your Boss: OK. Keep me informed and let me know if there is anything else I can do.

You: There is actually one more thing. See, this is very personal, and I don't really want other people here to know about it yet. Could we just keep this between ourselves for now?

Your Boss: That seems reasonable. Again, let me know how you are doing and if anything changes.

You: That's great. I knew you would understand, and I really appreciate it. Just for your records, I've written down what we just discussed in this letter to you. If you have any more questions about my hepatitis you can review this letter or please feel free to ask me.

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hands thoroughly after using the bathroom and before meals. If others see that you're being extra careful with your own hygiene, they'll be reassured that you're doing what you can to keep them healthy, too.

What are my legal rights?

This section provides a general overview of some federal laws which may apply to your situation. Many states have laws which provide similar protection. For specific advice as to any particular situation, you should contact a lawyer in your area. If you do not know how to find a lawyer, the local Bar association may be able to help.

Deciding to tell your boss or your coworkers about your hepatitis is a troubling question, but for most people, the most important thing is finding a way to stay at work, despite their illness. Under the ADA, your employer must help you find ways to try to accommodate your disability if it starts to interfere with your job. That means that you and your boss must together come up with ways that you can keep working, despite your illness, without disrupting the business. Your employer is not required to spend a lot of money to give you an entirely different workplace, or give most of your responsibilities to other workers. He or she is also not required to change the basic requirements of your job.

To claim your rights under the ADA, you must still be able to perform the essential functions of your job. For example, a waitress must still be able to remember orders and deliver food to customers' tables; a machinist must still be able to operate the tools and keep up with the production line; or a computer programmer must still be able to type, attend meetings, and meet project deadlines. Each situation is different and has to be considered on its own.

Usually, you can work with your supervisor to come up with creative ways to continue to do your job despite the impact of hepatitis on your energy level and schedule. For instance, if you are struggling with nausea, you might ask for an exception to a rule stating that you can't have food at your desk so that you can snack on some dry crackers and tea throughout the day. Other reasonable changes might include flex time, shorter workdays, or perhaps allowing you to take some work home so you can go to outpatient therapy or get additional rest at home as you are getting used to a new drug treatment.

However, in order for you to get

THE BASICS OF THE AMERICANS WITH DISABILITIES ACT

The Americans with Disabilities Act (ADA) defines a disability as a "physical or mental impairment that substantially limits one or more of the person's major life activities." (Note: Employers with fewer than 15 employees do not have to follow the ADA.) Under the ADA, your employer cannot discriminate against you because you have hepatitis by:

- Limiting your opportunities or status
- Starting company policies that will discriminate against you
- Refusing to give you benefits
- Not making reasonable changes, called accommodations, to help you continue to do your job
- Using your illness as an excuse to prevent you from doing some aspect of your job
- Using a pre-employment test that intends to determine something about your illness rather than whether you can do the job you're applying for

Good ← to know!

EXHIBIT 3

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solution. However, keep in mind that if you change your official job status from permanent full time to permanent part time, you may also change your insurance coverage, retirement plan, and other benefits. Company policies may be less flexible for part-timers than for full-timers. It may be difficult to switch back to full-time status. If your medical condition gets worse and you need to apply for Social Security Disability Insurance (SSDI), you may not qualify for full SSDI payments if your last permanent job was part time.

Be sure to find out all the details of part-time status from the human resource department before you make the switch. Perhaps you can arrange a temporary reduction in hours (and pay) that will let you keep your full benefits while you're recovering from hepatitis symptoms or treatment.

. . . if you change your official job status from permanent full time to permanent part time, you may also change your insurance coverage, retirement plan, and other benefits.

Can I use the Family Leave Act?

The Family Medical Leave Act (FMLA) says that if you have worked for your company full time for at least a year, you are allowed to take up to 12 weeks of unpaid time off every year (either on consecutive days or on an intermittent basis) to take care of your own serious medical needs. (Your spouse, child, or parent could also claim time under the FMLA to take care of you if you are seriously ill.) If you return within 12 weeks or your period of absence does not exceed 12 weeks, under the Act your employer must give you your job (or an equivalent job) back when you return. Make sure you talk to your boss about the FMLA, and whether it applies to you, before you take the time off. Again, many states have laws which provide similar protection. For any particular situation you should consult a lawyer in your area.

If you think that your employer isn't willing to be as accommodating as you want in adjusting your workplace, you can contact the local office of the Equal Employment Opportunity Commission (EEOC), which handles ADA complaints, to look at your situation. (See the Resource List to find out how to contact the EEOC.)

You can also contact the Department of Justice, which operates the ADA Mediation Program. The Mediation Program provides federal mediators, or peacemakers, to try to work out such disagreements. (See the Resource List under the Americans with Disabilities Act Information Line to learn how to contact the Department of Justice in your region or the central office in Washington, D.C.) Every state has at least one mediator to step in and help. If that is not successful, you may still be able to sue under the provisions of the ADA.

Condition," on page 84, for tips on making documentation easier.) It can be frustrating, but try to be patient with the process. It may take months for your case to work through the Social Security system. If you're asked to provide additional information, do so without delay. The time you waste is yours, not theirs!

Planning for long-term financial security

Many people with hepatitis live with it for decades, so it's important to think through your long-term plans. The best time to deal with these issues is when you're feeling well. It's hard to spend those energetic days taking care of legal and money issues, but you'll be glad you did. Start to do this as soon as possible after you learn about your disease.

Keep saving for retirement. It's more important than ever to be sure that you'll have enough money to live on, especially because your medical expenses may be higher than you'd anticipated. Get details from your employer's human resources department about how you can put more money into your company's pension, profit-sharing, or retirement savings plan. You may want to consult with a certified financial planner to be sure that you have considered every retirement-planning option.

You may also have to change your expectations about how you run your household. Is your house or apartment too big or too cluttered to take care of yourself when you're ill? You could save money, and gain convenience, by reorganizing your belongings or shutting down some rooms. You may even want to consider moving into a smaller place. This is also a good time to think about how you will feel traveling regularly from your home to your doctor's office when you are ill. Is this a convenient trip now? Or is it long and/or expensive?

Finally, make certain that you understand your health insurance benefits, and what you need to do to keep them. If you do not have health insurance, there are strict regulations

QUIZ

Q. ***What is the best way to speak to people about your illness?***

A. **First, make sure you trust them or that you must tell them for legal reasons. Then approach them directly, answer their questions without a fuss, and emphasize that you're carrying on as well as you can.**

Q. ***Does the ADA guarantee that my boss has to let me keep my job?***

A. **Not necessarily. The law requires your employer to make reasonable accommodations for people with disabilities — not totally rearrange the workplace. You must still be able to do your job.**

Q. ***What are disability payments, and who can get them?***

A. **Disability payments are monies given by the U.S. government to people who have certain mental or physical problems.**

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Research Offers Hope for the Future

So far, we've concentrated on information about current treatments that will help manage your disease and your life now that you have been diagnosed with hepatitis, and to protect your loved ones and others from contracting the virus. Now we're going to talk about new treatments that may be available to help you in the future.

The search for new treatments for hepatitis B and hepatitis C has been slow and sometimes frustrating. But new treatments are being tried.

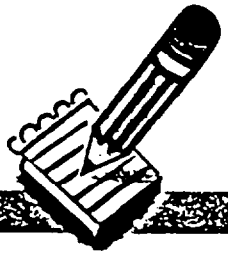
Any one of the ideas being pursued by researchers today could be the next breakthrough in treating hepatitis. Yet the fact is that while some will work better than others, some may not work at all, and no one can pick the winners until all of the research information is studied.

How better diagnosis can improve treatment

As well as new treatments, researchers are working on new types of tests that can give your doctor more information about both the virus that has infected you and how your body is reacting to the infection. Together, this information can steer you and your doctor toward the best treatments for you.

For example, certain genotypes (slightly different strains of the same virus) of hepatitis C can be attacked more effectively by interferon than others.

Researchers have also found that people whose bodies are producing large numbers of immune cells, called cytotoxic cells or sometimes called killer cells, seem to have the best ability to clear the hepatitis B virus from their systems. More research may provide more information about these viruses.



KEY WORDS & QUESTIONS

EXHIBIT 3

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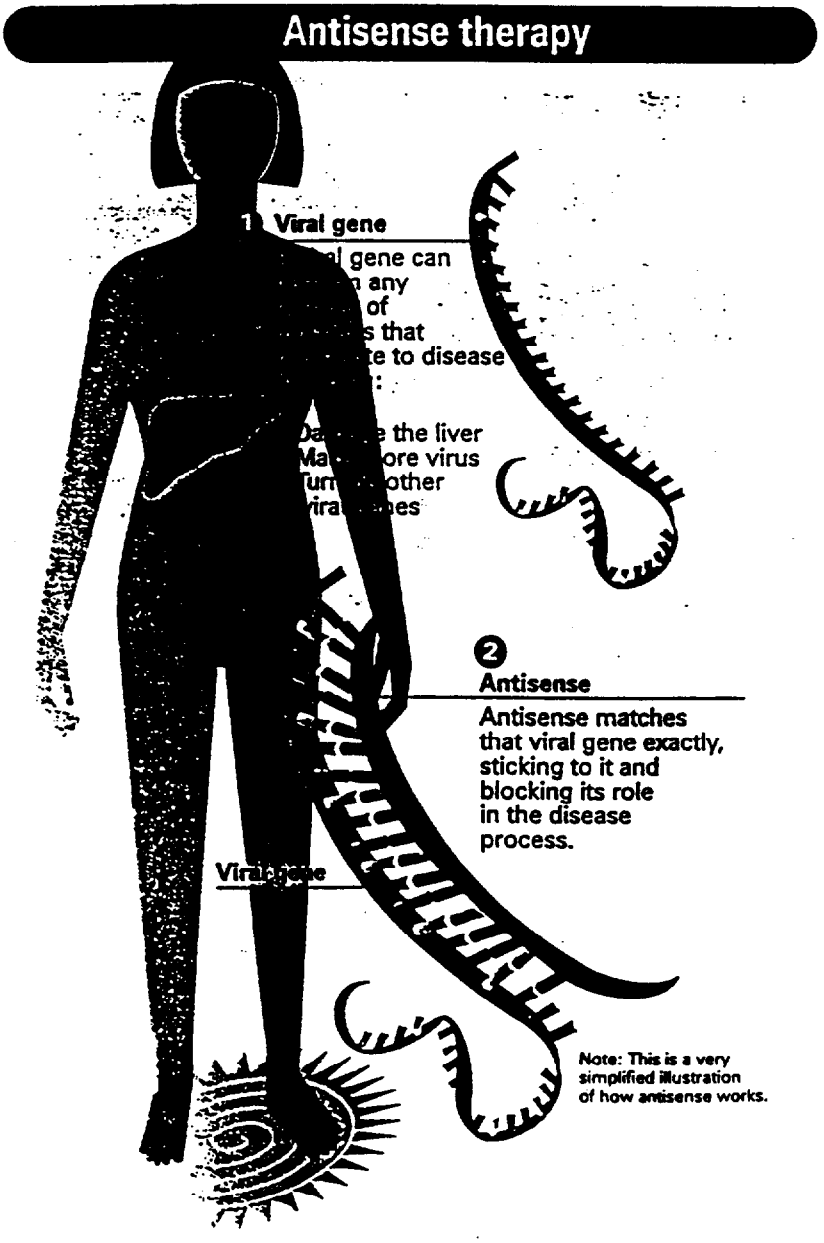
presents vaccine developers with a moving target. Once in the body, hepatitis C can literally change its coat in a process known as mutation. A mutation is a permanent change to the virus's genetic make-up. This change also affects the virus's outer coat, or capsule. (Because the coat around the virus is what helps the body detect and then attack it, clearing the virus from the body is a little like a game of hide and seek.)

Hepatitis C mutates more rapidly than hepatitis B or HIV. So much so, in fact, that the body ends up having to fight many, many slightly different mutations of hepatitis C. This has made producing a vaccine for hepatitis C difficult. (See illustration on page 93.)

A vaccine against the virus would probably need to protect against many strains at once, or you would need several vaccines. Research in the related problem of figuring out how to protect people from the many strains of the flu or the AIDS virus, other organisms that mutate a lot, may offer some clues that will help with hepatitis C as well.



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One type of gene therapy being planned for viral hepatitis is called antisense therapy. Most people think of gene therapy as being a way to put a good gene (one that works) into a cell that has a bad gene (one that doesn't work), but antisense is a completely different approach that aims to just shut off bad genes (in this case, those of a virus). In antisense, the patient is given a man-made copy of DNA that is exactly matched to a gene that the virus needs to reproduce itself. The antisense DNA attaches to the viral gene (or to another molecule that the cell uses to make proteins), interfering with its workings, and preventing the virus from surviving. (See illustration on page 94.)

The next step

The sheer number of new approaches being tried in viral hepatitis therapy is encouraging. The fact that researchers are using new knowledge to aim these approaches more effectively is even better.

As you move ahead with your treatment of hepatitis, keep in mind that you have already taken two important steps by seeking medical care and by reading this book to learn more about the virus. You have probably written down several questions to ask your doctor. Be sure to note the answers you receive. Also, you now know how to speak with your loved ones and boss about this disease, something that may have felt uncomfortable before. Do refer to this book whenever you have questions about the disease or to reread the action steps. Remember, there are many ways that you can be in charge of your hepatitis. ▼

EXHIBIT 3

Support groups and hotlines

American Liver Foundation (Hepatitis and Liver Disease Hotline)

1425 Pompton Ave.
Cedar Grove, NJ 07009
1-800-465-4837, 1-800-443-7222
Hours: 9 AM–7:30 PM, Monday–Friday, Eastern Time
Languages: English and Spanish
A great source for information and support groups.

Centers for Disease Control and Prevention (CDC)

1600 Clifton Rd. NE
Atlanta, GA 30333
1-404-332-4555
Hours: 8 AM–4:30 PM (except holidays), Monday–Friday, Eastern Time
Call to hear recorded messages about different diseases including hepatitis. Information can be faxed to you.

The Hepatitis C Foundation

1502 Russett Drive
Warminster, PA 18974
1-215-672-2606
Fax: 1-215-672-1518
Hours: 9 AM–5 PM, Monday–Friday
If you are faced with hepatitis in any capacity, contact this group for support and information.

Hep C Connection

1177 Grant St.
Denver, CO 80203
1-800-522-HEPC (1-800-522-4372)
1-303-860-0800 (Colorado residents)
Call for referrals to support groups in your area, if one exists.

HIV/AIDS Clinical Trials Information Service

P.O. Box 6421
Rockville, MD 20849-6421
1-800-874-2572
Languages: English or Spanish
Hours: 9 AM–7 PM, Eastern Time
If you have HIV and a related disease such as hepatitis, call for information and referrals.

National HIV/AIDS Hotline

1-800-342-2437
Hours: 24 hours a day, including holidays
Call if you have HIV or AIDS.

National Council for Reliable Health Information

300 E. Pink Hill
Independence, MO 64057
1-816-228-4595
Hours: 8 AM–5 PM, Monday–Friday; Central Time
Call for information about specific alternative therapies.

Project Inform National HIV/AIDS Treatment Hotline

1965 Market St., Suite 220
San Francisco, CA 94103
1-800-822-7422
Hours: 9 AM–5 PM, Monday–Friday; 10 AM–4 PM, Saturday, Pacific Time
Languages: Primarily English, some Spanish
Phone for information on treatment of HIV and its relation to other diseases.

Disability-related resources

Equal Employment Opportunity Commission (EEOC)

JFK Federal Building, 4th Floor
Boston, MA 02203
1-800-669-4000
Hours: 8:30 AM–5 PM, Eastern Time
Languages: French, German, Spanish, Italian, and English
Handles complaints about disability rights issues in the workplace.

The Americans with Disabilities Act Information Line

Disability Rights Section,
Civil Rights Division
U.S. Department of Justice
P.O. Box 66738
Washington, DC 20035-6738
1-800-514-0301
Hours: 10 AM–6 PM, Monday–Wednesday and Friday; 1 PM–6 PM Thursday (except holidays)
Eastern Time
Automated System 24 hours a day
Languages: Spanish and English
Provides guidance on disability rights issues.

Social Security Administration

1-800-772-1213
Languages: Spanish and English
Call to find out about disability payments.

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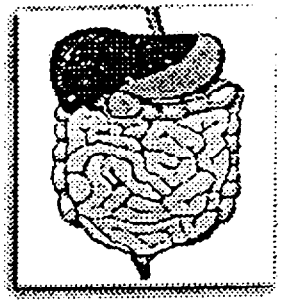


Chronic Hepatitis C: Current Disease Management

NIDDK National Digestive Diseases Information Clearinghouse

Publications
NIDDK

Also see:
Easy-to-Read
What Do I Need To Know About Hepatitis C?

Introduction

The hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the United States. It accounts for about 20 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and 30 percent of cirrhosis, end-stage liver disease, and liver cancer. Almost 4 million Americans, or 1.8 percent of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. Hepatitis C causes an estimated 8,000 to 10,000 deaths annually in the United States.

A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease. At least 75 percent of patients with acute hepatitis C ultimately develop chronic infection, and most of these patients have accompanying chronic liver disease.

Chronic hepatitis C varies greatly in its course and outcome. At one end of the spectrum are patients who have no signs or symptoms of liver disease and completely normal levels of serum liver enzymes. Liver biopsy usually shows some degree of chronic hepatitis, but the degree of injury is usually mild, and the overall prognosis may be good. At the other end of the spectrum are patients with severe hepatitis C who have symptoms, HCV RNA in serum, and elevated serum liver enzymes, and who ultimately develop cirrhosis and end-stage liver disease. In the middle of the spectrum are many patients who have few or no symptoms, mild to moderate elevations in liver enzymes, and an uncertain prognosis. Researchers estimate that at least 20 percent of patients with chronic hepatitis C develop cirrhosis, a process that takes 10 to 20 years. After 20 to 40 years,

EXHIBIT 3

sexually transmitted diseases.

- People who use cocaine, particularly with intranasal administration, using shared equipment.

Maternal-Infant Transmission

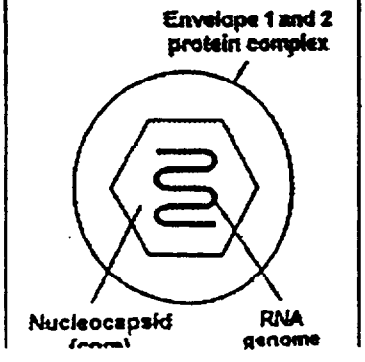
Maternal-infant transmission is not common. In most studies, only 5 percent of infants born to infected women become infected. The disease in newborns is usually mild and free of symptoms. The risk of maternal-infant spread rises with the amount of virus in the mother's blood. Breast-feeding has not been linked to HCV's spread.

Sexual Transmission

Sexual transmission of hepatitis C between monogamous partners appears to be uncommon. Whether hepatitis C is spread by sexual contact has not been conclusively proven, and studies have been contradictory. Surveys of spouses and monogamous sexual partners of patients with hepatitis C show that less than 5 percent are infected with HCV, and many of these have other risk factors for this infection. For this reason, changes in sexual practices are not recommended for monogamous patients. Testing sexual partners for anti-HCV can help with patient counseling. People with multiple sex partners should be advised to follow safe sex practices, which should protect against hepatitis C as well as hepatitis B and HIV.

Sporadic Transmission

Sporadic transmission, when the source of infection is unknown, occurs in about 10 percent of acute hepatitis C cases and in 30 percent of chronic hepatitis C cases. These cases are also referred to as sporadic or community-acquired infections. These infections may have come from exposure to the virus from cuts, wounds, or medical injections or procedures.



The Hepatitis C Virus

HCV is a small (40 to 60 nm in diameter), enveloped, single-stranded RNA virus of the family Flaviviridae. Because the virus mutates rapidly, changes in the envelope protein may help it evade the immune system. There are at least 6 major genotypes and more than 50 subtypes of HCV. The different genotypes have different geographic distributions. Genotypes 1a

EXHIBIT 2

- Kidney disease
- Neuropathy
- Cryoglobulins, rheumatoid factor, and low complement levels in serum.

Other complications of chronic hepatitis C are

- Glomerulonephritis
- Porphyria cutanea tarda.

Diseases that are less well documented to be related to hepatitis C are

- Seronegative arthritis
- Keratoconjunctivitis sicca (Sjögren's syndrome)
- Non-Hodgkin's type, B-cell lymphomas
- Fibromyalgia
- Lichen planus.

Serologic Tests

Enzyme Immunoassay

Anti-HCV is detected by enzyme immunoassay (EIA). The third-generation test (EIA-3) used today is more sensitive and specific than previous ones. However, as with all enzyme immunoassays, false-positive results are occasionally a problem with the EIA-3. Additional or confirmatory testing is often helpful.

The best approach to confirm the diagnosis of hepatitis C is to test for HCV RNA using a sensitive polymerase chain reaction (PCR) assay. The presence of HCV RNA in serum indicates an active infection. Testing for HCV RNA is also helpful in patients in whom EIA tests for anti-HCV are unreliable. For instance, immunocompromised patients may test negative for anti-HCV despite having HCV infection because they may not produce enough antibodies for detection with EIA. Likewise, patients with acute hepatitis may test negative for anti-HCV when the physician first tests. Antibody is present in almost all patients by 1 month after onset of acute illness; thus, patients with acute hepatitis who initially test negative may need followup testing. In these situations, HCV RNA is usually present and confirms the diagnosis.

Infection

- In chronic hepatitis C, increases in the alanine and aspartate aminotransferases range from 0 to 20 times (but usually less than 5 times) the upper limit of normal.
- Alanine aminotransferase levels are usually higher than aspartate aminotransferase levels, but that finding may be reversed in patients who have cirrhosis.
- Alkaline phosphatase and gamma glutamyl transpeptidase are usually normal. If elevated, they may indicate cirrhosis.
- Rheumatoid factor and low platelet and white blood cell counts are frequent in patients with cirrhosis, providing clues to the presence of advanced disease.
- The enzymes lactate dehydrogenase and creatine kinase are usually normal.
- Albumin levels and prothrombin time are normal until late-stage disease.
- Iron and ferritin levels may be slightly elevated.

Quantification of HCV RNA in Serum

Several methods are available for measuring the titer or level of virus in serum, which is an indirect assessment of viral load. These methods include a quantitative PCR and a branched DNA (bDNA) test. Unfortunately, these assays are not standardized, and different methods from different laboratories can provide different results on the same specimen. In addition, serum levels of HCV RNA can vary spontaneously by 3- to 10-fold over time. Nevertheless, when performed carefully, quantitative assays provide important insights into the nature of hepatitis C. Viral load does not correlate with the severity of the hepatitis or with a poor prognosis (as it seems to in HIV infection); but viral load does correlate with the likelihood of a response to antiviral therapy. Rates of response to a course of alpha interferon and ribavirin are higher in patients with low levels of HCV RNA. There are several definitions of a "low level" of HCV RNA, but the usual definition is below 2 million copies per milliliter (mL).

In addition, monitoring viral load during the early phases of treatment may provide early information on the likelihood of a

HCV causes the following changes in liver tissue:

- Necrosis and inflammation around the portal areas, so-called "piecemeal necrosis" or "interface hepatitis."
- Necrosis of hepatocytes and focal inflammation in the liver parenchyma.
- Inflammatory cells in the portal areas ("portal inflammation").
- Fibrosis, with early stages being confined to the portal tracts, intermediate stages being expansion of the portal tracts and bridging between portal areas or to the central area, and late stages being frank cirrhosis characterized by architectural disruption of the liver with fibrosis and regeneration.

Grading and staging of hepatitis by assigning scores for severity are helpful in managing patients with chronic hepatitis. The degree of inflammation and necrosis can be assessed as none, minimal, mild, moderate, or severe. The degree of fibrosis can be similarly assessed. Scoring systems are particularly helpful in clinical studies on chronic hepatitis.

Immuno-staining

Immunostaining using polyclonal or monoclonal antibodies to detect HCV antigens in the liver has been reported to be useful. However, these tests are not commercially available, and, even in the hands of research investigators, immunostaining detects HCV antigens in liver tissue in only 60 to 70 percent of patients with chronic hepatitis C--largely in those with high levels of HCV in serum. This test also requires special handling of liver tissue and thus is not appropriate for routine clinical use.

Diagnosis

Hepatitis C is most readily diagnosed when serum aminotransferases are elevated and anti-HCV is present in serum. The diagnosis is confirmed by the finding of HCV RNA in serum.

Acute Hepatitis C

Acute hepatitis C is diagnosed on the basis of symptoms such as jaundice, fatigue, and nausea, along with marked increases in serum ALT (usually greater than 10-fold elevation), and presence of anti-HCV or de novo development of anti-HCV.

Diagnosis of acute disease can be problematic because anti-HCV is not always present when the patient presents to the physician with

Combination therapy consistently yields higher rates of sustained response than monotherapy. Combination treatment is more expensive and is associated with more side effects than monotherapy, but, in most situations, it is preferable. At present, interferon monotherapy should be reserved for patients who have contraindications to the use of ribavirin.

Several forms of alpha interferon are available (alfa-2a, alfa-2b, and consensus interferon). These interferons are given subcutaneously three times weekly in doses of 3 million units (MU) or, in the case of consensus interferon, 9 µg per injection. Ribavirin, in contrast, is an oral antiviral agent that is given twice a day in 200-mg capsules for a total daily dose of 1,000 mg for patients who weigh less than 75 kilograms (165 pounds) or 1,200 mg for those who weigh more than 75 kilograms.

Treatment with interferon alone or combination therapy with interferon and ribavirin leads to rapid improvements in serum ALT levels in 50 to 75 percent of patients and the disappearance of detectable HCV RNA from the serum in 30 to 50 percent. However, a long-term improvement in liver disease usually occurs only if HCV RNA disappears during therapy and stays undetectable when therapy is stopped.

A response is considered to be "sustained" if HCV RNA remains undetectable for 6 months or more after therapy stops. With interferon monotherapy, 30 to 35 percent of patients become HCV RNA negative with treatment, but almost half of these relapse when treatment stops: The sustained response rate, therefore, averages only 15 to 20 percent. Combination therapy with interferon and ribavirin, however, leads to loss of HCV RNA on treatment in 50 to 55 percent of patients and a sustained loss in 35 to 45 percent. Thus, combination treatment results in both a higher rate of loss of HCV RNA on treatment and a lower rate of relapse when treatment is stopped.

The optimal duration of treatment varies depending on whether interferon monotherapy or combination therapy is used, as well as by HCV genotype. For patients treated with interferon monotherapy, a 48-week course is recommended, regardless of genotype. For patients treated with combination therapy, the optimal duration of treatment depends on viral genotype. Patients with genotypes 2 and 3 have a high rate of response to combination treatment (60 to 70 percent), and a 24-week course of combination therapy yields results equivalent to those of a 48-week course. In contrast, patients with genotype 1 have a lower rate of response to combination therapy (25 to 35 percent), and a 48-week course yields a significantly better sustained response rate. Again, because

should be reassessed at regular intervals. In view of the rapid developments in hepatitis C today, better therapies may become available within the next few years, at which point expanded indications for therapy would be appropriate.

In patients with clinically significant extrahepatic manifestations, such as cryoglobulinemia and glomerulonephritis, therapy with alpha interferon can result in remission of the clinical symptoms and signs. However, relapse after stopping therapy is common. In some patients, continual, long-term alpha interferon therapy can be used despite persistence of HCV RNA in serum if clinical symptoms and signs resolve on therapy.

Who Should Not Be Treated?

Therapy is inadvisable outside of controlled trials for patients who have

- Clinically decompensated cirrhosis because of hepatitis C.
- Normal aminotransferase levels.
- A kidney, liver, heart, or other solid-organ transplant.
- Specific contraindications to either monotherapy or combination therapy.

Contraindications to alpha interferon therapy include severe depression or other neuropsychiatric syndromes, active substance or alcohol abuse, autoimmune disease (such as rheumatoid arthritis, lupus erythematosus, or psoriasis) that is not well controlled, bone marrow compromise, and inability to practice birth control. Contraindications to ribavirin and thus combination therapy include marked anemia, renal dysfunction, and coronary artery or cerebrovascular disease, and, again, inability to practice birth control.

Alpha interferon has multiple neuropsychiatric effects. Prolonged therapy can cause marked irritability, anxiety, personality changes, depression, and even suicide or acute psychosis. Patients particularly susceptible to these side effects are those with preexisting serious psychiatric conditions and patients with neurological disease. Interferon therapy is also associated with relapse in people with a previous history of drug or alcohol abuse. Alpha interferon should not be given to a patient who has only recently stopped alcohol or substance abuse. Typically a 2-year abstinence is recommended before starting therapy. Strict abstinence from alcohol is recommended during therapy with interferon.

EXHIBIT 3

- Skin irritation at the injection site
- Low-grade fever
- Weight loss
- Irritability
- Depression
- Mild bone marrow suppression
- Hair loss (reversible).

Most of these side effects are mild to moderate in severity and can be managed. They are worse during the first few weeks of treatment, especially with the first injection. Thereafter, side effects diminish. Acetaminophen may be helpful for the muscle aches and low-grade fever, and side effects may be less troublesome if interferon is taken in the evening. Fatigue and depression are occasionally so troublesome that the dose of interferon should be decreased or therapy stopped early. Depression and personality changes can occur on interferon therapy and be quite subtle and not readily admitted by the patient. These side effects need careful monitoring.

Ribavirin also causes side effects, and the combination is generally less well tolerated than interferon monotherapy. The most common side effects of ribavirin are

- Anemia
- Fatigue and irritability
- Itching
- Skin rash
- Nasal stuffiness, sinusitis, and cough.

Ribavirin causes a dose-related hemolysis of red cells; with combination therapy, hemoglobin usually decreases by 2 to 3 gm/dL and the hematocrit by 5 to 10 percent. The amount of decrease in hemoglobin is highly variable. The decrease starts between weeks 1 and 4 of therapy and can be precipitous. Some patients develop symptoms of anemia, including fatigue, shortness of breath, palpitations, and headache.

EXHIBIT 3

complication have required corticosteroid therapy to control the hepatitis.

Options for Patients Who Do Not Respond to Treatment

Few options exist for patients who either do not respond to therapy or who respond and later relapse. Patients who relapse after a course of interferon monotherapy may respond to a 24-week course of combination therapy, particularly if they became and remained HCV RNA negative during the period of monotherapy. Another approach is the use of long-term or continual interferon, which is feasible only if the interferon is well tolerated and has a clear-cut effect on serum aminotransferases and liver histology, despite lack of clearance of HCV RNA. New medications and approaches to treatment are needed. Most promising for the immediate future are newer forms of "long-acting" interferons, which are alpha interferons that are modified by polyethylene glycol (PEG) so that they can be given once a week and yet provide a sustained level of interferon. These "pegylated" formulations may avoid the peaks and troughs of interferon levels and interferon side effects that occur when it is given three times a week. Pegylated interferons are now being evaluated in prospective controlled trials. Other promising approaches are the use of other cytokines and the development of newer antivirals, such as RNA polymerase, helicase, or protease inhibitors.

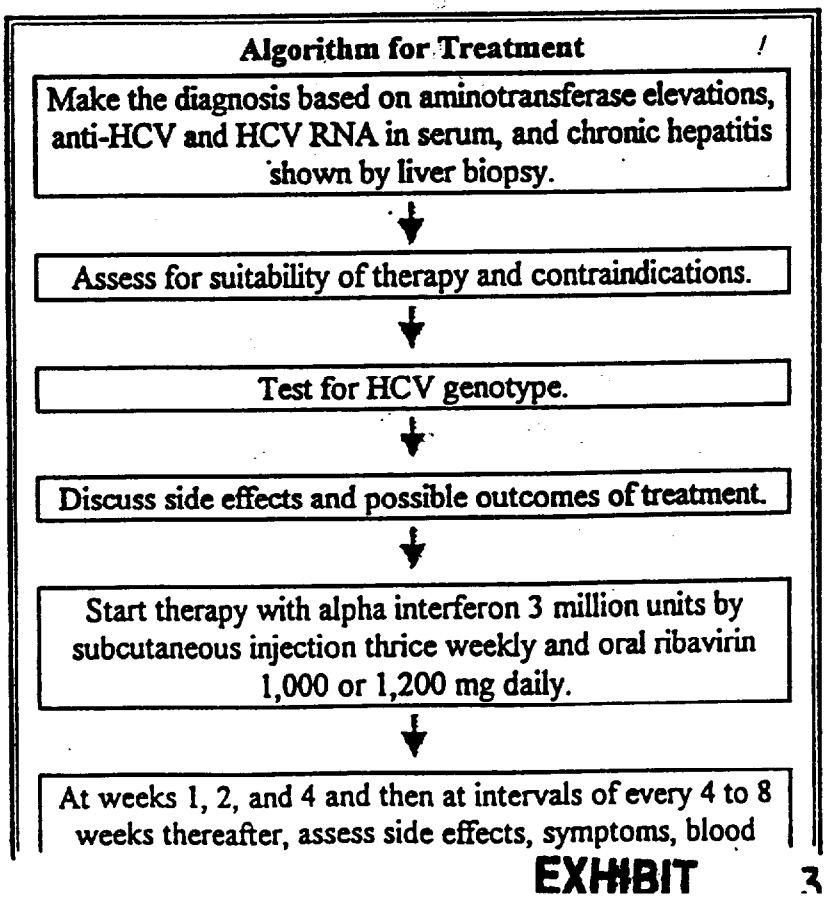


EXHIBIT 3

ribavirin if severe anemia occurs (hemoglobin < 8.5 gm/dL or hematocrit < 26 percent).

- Measure HCV RNA by PCR at 24 weeks. If HCV RNA is still present, stop therapy. If HCV RNA is negative and patient had genotype 1 (1a or 1b), continue therapy for another 24 weeks.
- Reinforce the need to practice strict birth control during therapy and for 6 months thereafter.
- Measure thyroid-stimulating hormone levels every 3 to 6 months during therapy.
- At the end of therapy, test HCV RNA by PCR to assess whether there is an end-of-treatment response.

After Therapy

- Measure aminotransferases every 2 months for 6 months.
- Six months after stopping therapy, test for HCV RNA by PCR. If HCV RNA is still negative, the chance for a long-term "cure" is excellent; relapses have rarely been reported after this point.

The Future of Hepatitis C: Research

Basic Research

A major focus of hepatitis C research is developing a tissue culture system that will enable researchers to study HCV outside the human body. Animal models and molecular approaches to the study of HCV are also important. Understanding how the virus replicates and how it injures cells would be helpful in developing a means of controlling the virus and in screening for new drugs that would block it.

Diagnostic Tests

More sensitive and less expensive assays for measuring HCV RNA and antigens in the blood and liver are needed. Although current tests for anti-HCV are quite sensitive, a small percentage of patients with hepatitis C test negative for anti-HCV (false-negative reaction), and a percentage of patients who test positive are not infected (false-positive reaction). Also, there are patients who have resolved the infection but still test positive for anti-HCV.

http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/httoc.htm

Centers for Disease Control and Prevention. (1998). Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *Morbidity and Mortality Weekly Report, 47,* 1-39.

Hoofnagle, J. H., & Di Bisceglie, A. M. (1997). The treatment of chronic viral hepatitis. *New England Journal of Medicine, 336* (5), 347-356.

Lemon, S. M., & Thomas, D. L. (1997). Vaccines to prevent viral hepatitis. *New England Journal of Medicine, 336* (5), 196-204.

McDonnell, W. M., & Lok, A. S. (1996). Testing for hepatitis C virus RNA in serum: When and how? *Viral Hepatitis Reviews, 2* (2), 81-83.

McHutchison, J. G., Gordon, S. C., Schiff, E. R., et al. (1998). Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis. *New England Journal of Medicine, 339*(21), 1485-1492.

Proceedings of the National Institutes of Health Consensus Development Conference (1997). Management of hepatitis C. *Hepatology, 26* (Supplement 1).

Strader, D. B., & Seeff, L. B. (1996). The natural history of chronic hepatitis C infection. *European Journal of Gastroenterology & Hepatology, 8*(4), 324-328.

Patient Education Resources

The National Digestive Diseases Information Clearinghouse (NDDIC) has patient education materials on hepatitis C. To obtain free copies, contact the clearinghouse at

NDDIC
2 Information Way
Bethesda, MD 20892-3570
E-mail: nddic@info.niddk.nih.gov

Patient education materials are also available from

American Liver Foundation
1425 Pompton Avenue
Cedar Grove, NJ 07009-1000
Tel: (800) 223-0179 or (201) 256-2550

Hepatitis Foundation International

EXHIBIT 3

Side Effects of Alpha Interferon in Chronic Hepatitis C

GEOFFREY DUSHEIKO

Alpha interferons have been used widely to treat chronic hepatitis C virus infection. These include recombinant interferons, purified natural leukocyte, and lymphoblastoid interferons. Alpha interferon is administered by subcutaneous or intramuscular injection either daily or three times weekly for a period of 6 to as long as 24 months. A wide array of adverse effects of alpha interferon have been described. Several side effects such as fever, headache fatigue, arthralgias, and myalgias are common, especially with the initial injections. These early side effects of interferon are predictable and are encountered in the majority of patients. These may not require dose modification, but can be problematic for a significant proportion of patients. Other adverse events effects may require dose modification or even discontinuation of therapy in 2% to 10% of patients. Neuropsychiatric side effects such as depression and irritability can be most troublesome; their mechanisms are not well understood. Granulocytes, platelets, and red blood cell counts decrease during treatment, but the decreases are usually mild, although they can be dose limiting if cell counts are low initially. Interferon has important immunomodulatory properties, and treatment can induce autoimmune phenomena, the most frequent being autoimmune thyroiditis with either hypothyroidism or hyperthyroidism, especially in predisposed patients. Other autoimmune disease can be aggravated by interferon therapy. Severe and even life-threatening side effects of interferon occur in 0.1% to 1% of patients; these include thyroid, visual, auditory, renal, and cardiac impairment, and pulmonary interstitial fibrosis. Some of these side effects may be irreversible. Higher doses of interferon (above 5 million units three times weekly) cause higher rates of adverse events than standard doses. Contraindications to alpha interferon have been recognized. (HEPATOLOGY 1997; 26(Suppl 1):112S-121S.)

Alpha interferon is a cytokine with pleotropic activities that include potent antiviral and antiproliferative effects, as well as many adverse side effects. Binding of type 1 interferon to a cell surface receptor leads to the intracellular production of several gene products. Many of these interferon-induced genes, including 2′,5′-oligoadenylate synthetase and β2-microglobulin, are accepted surrogate markers for the biological activity of interferon. Which of these proteins is responsible for the antiviral activities and which for the side effects of alpha interferon in chronic hepatitis C is not known.

Alpha interferon is available worldwide as at least six different products made by as many pharmaceutical companies. It is approved for human use in the European Union and the United States for several medical conditions, including hairy cell leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, condylomata acuminata, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, basal cell carcinoma, chronic hepatitis B, and chronic hepatitis C. Both recombinant as well as lymphoblastoid and natural leukocyte alpha interferons have been used to treat chronic hepatitis C virus infection.

PHARMACOKINETIC DATA

Alpha interferon is usually administered by subcutaneous or intramuscular injection. Maximum serum levels occur 3 to 12 hours after injection, and serum levels are usually below the limit of detection by 16 hours.[1] The elimination half-life of interferon after both subcutaneous and intramuscular injections is 2 to 3 hours, and clearance from the systemic circulation is primarily by renal catabolism. After intravenous administration, serum levels of interferon are maximal at the end of the infusion, becoming undetectable within 4 hours of the infusion. The elimination half-life is approximately 2 hours. Measurement of serum concentrations of different preparations of alpha interferon is problematical because the levels achieved are low after injection of typical doses of 3 to 10 million units (MU).

TOXICOLOGY

The alpha interferons are generally species specific.[2] Thus, animal toxicology studies of human interferon are not very meaningful. Toxicology studies using human and animal interferons have been completed in mice, rats, rabbits, and monkeys. Animal reproduction studies indicate that murine alpha interferon is not teratogenic in rats or rabbits and does not affect pregnancy, fetal development, or reproductive capacity in offspring of treated rats. It is not clear whether these findings can be extrapolated to humans or whether alpha interferon can cross the placental barrier, but the bulk of evidence suggests that interferon does not.[2]

The mechanisms for clinical toxicity caused by alpha interferon are poorly understood. Inducible biochemical markers, such as 2′,5′-oligoadenylate synthetase activity, correlate well with dose administered and serum concentrations of interferon, but correlate poorly with clinical response and frequency of side effects.[1]

ADVERSE EFFECTS OF ALPHA INTERFERON

What is known of the clinical toxicology of interferon has been derived from clinical experience and safety data within therapeutic trials. This review focuses on adverse events reported in therapeutic trials of interferon, study monitoring

Abbreviation: MU, million units.

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matocrit, which tend to stabilize after the first 3 months of therapy, occur frequent during interferon therapy. A decrease from baseline of ≥20% has been observed in approximately 1% of patients. The decrease in blood counts tends to be reversible with dose reductions, at least in part. In the large comparative trial of consensus interferon and interferon alfa-2b, the average decrease in white blood cell counts was 19% at the end of treatment, which reverted to normal after therapy. Polymorphonuclear cell counts decreased by 23% and platelet counts by 16% at the end of treatment, but both returned to baseline by the end of observation. Decreases in platelet counts to less than 50,000/μL occurred in 3% of patients treated with 9 μg of consensus interferon.

Interferon therapy has been reported to affect serum lipids. An increase in mean serum triglyceride concentrations is common (35%) during treatment. These abnormalities reverse with discontinuation of therapy.[21-24]

Alpha interferon may have mild renal effects. Asymptomatic and mild proteinuria is relatively common during the first few days of interferon therapy, perhaps as a result of fever. Nephrotic syndrome and severe renal injury of interferon are rare.

SEVERE ADVERSE EVENTS

Fatal and life-threatening side effects from alpha interferon therapy are rare with the doses used to treat chronic hepatitis C. The best estimate of the frequency of severe adverse events with interferon therapy derives from a large, retrospective survey conducted in 73 Italian centers on a total of 11,241 patients with either chronic hepatitis B or C.[9] Among this large cohort, only five patients (0.04%) died because of complications of therapy, all five developing either liver failure or sepsis. Life-threatening side effects occurred in another eight patients (0.07%), which included depression leading to attempted suicide and bone marrow suppression with granulocyte count less than 500/μL or platelet counts less than 25,000/μL. Serious but not life-threatening side effects occurred in 131 patients (1.2%); these included symptomatic thyroid disease (n = 71), impotence (n = 5), systemic autoimmune disease (n = 5), immune-mediated dermatological diseases (n = 14), diabetes mellitus (n = 10), cardiovascular disease (n = 7), psychosis (n = 10), seizures (n = 4), peripheral neuropathy (n = 3), and hemolytic anemia (n = 2). Most of these complications were reversible. Thus, serious side effects occurred in 1 of 100 patients and fatal or life-threatening side effects in 1 of 1,000 patients.

In a Japanese study using high doses of interferon for chronic hepatitis C,[20] 8% of 677 patients who received 6 to 10 MU three times weekly for 24 weeks developed a serious complication of therapy. Five patients developed diabetes mellitus, 12 hyperthyroidism, and six hypothyroidism. In this series of patients, three developed interstitial pneumonia, one acquired a systemic lupus erythematosus-like syndrome, two had autoimmune hepatitis, two developed rheumatoid arthritis, and one developed autoimmune thrombocytopenic purpura. One patient experienced sudden hearing impairment. Symptoms of depression were observed in 23 patients.

In some patients, the common and predictable influenza-like side effects become severe and necessitate a reduction in dose or stopping treatment. Severe fatigue, marked cognitive and neuropsychiatric changes, including confusion, depression, paranoia or phobic anxiety, can occur during therapy. However, more common and more likely to lead to reduction in dose are irritability, sadness, emotional lability and moodiness (Table 2). Confusion, vertigo, paraesthesias and tinnitus have been reported. Other relatively common side effects that may require dose reduction include an increase in non–organ-specific antibodies, autoimmune thyroiditis, hyperthyroidism, autoimmune hepatitis, worsening diabetes mellitus, psoriasis, injection site reactions, or pruritus. Cardiac arrhythmias are relatively rare, but have been reported. Each of these side effects is discussed below by the organ system involved.

TABLE 2. Serious Adverse Events Reported With Alpha Interferon Therapy

Neuropsychiatric
Psychosis
Depression/suicide
Delirium
Confusion
Extrapyramidal-ataxia
Paresthesia
Seizures
Relapse in substance abuse
Immune disorders
Autoimmune thyroid disease
Autoimmune hepatitis
Systemic lupus erythematosis
Primary biliary cirrhosis
Septicaemia
Graft rejection
Skin
Psoriasis
Erythema multiforme
Systemic
Hepatic decompensation
Bleeding
Cardiac arrhythmias
Sudden death
Dilated cardiomyopathy
Hypotension
Acute renal failure
Other
Retinopathy
Hearing loss
Pulmonary interstitial fibrosis
Laboratory
Granulocytopenia
Thrombocytopenia
Anemia
Hyperthyroidism
Hypothyroidism

NEUROLOGICAL AND PSYCHIATRIC SIDE EFFECTS

The neuropsychiatric side effects of interferon can be troublesome and largely unpredictable. These side effects include fatigue, asthenia, drowsiness, lack of initiative, irritability, confusion, and apathy as well as other behavioral, emotional, mood, and cognitive changes. Paranoia, severe anxiety, or even psychosis may occur. The patient may have a change in personality that is often more discernible to members of their family than themselves. In a study from the National Institutes of Health,[25] 10 of 58 patients (17%) with chronic viral hepatitis treated with a 4- to 12-month course of recombinant alpha interferon developed psychiatric side effects.

EXHIBIT 3

oped thyroid dysfunction (five hypothyroidism and three hyperthyroidism) during treatment. All patients recovered within 1.5 years after stopping interferon treatment.[52,53] No pretreatment risk was identified.

Hyperthyroidism or hypothyroidism may not be reversible after stopping therapy. Stopping therapy early may help blunt the severity of illness. However, transient thyroid abnormalities of little clinical significance can also occur during therapy. Some patients also develop transient hyperthyroidism followed by prolonged hypothyroidism, with increases in serum tri-iodothyronine, thyroxine, and decreases in thyroid-stimulating hormone levels, soon followed by low tri-iodothyronine and thyroxine values and increased serum thyroid-stimulating hormone levels. Long-term thyroid replacement may be required for those who become hypothyroid.[55-57] It is possible that thyroid disease is more common in chronic hepatitis C infection independently of interferon therapy.

Interferon may also aggravate pre-existing thyroid dysfunction as well as induce disease in the absence of previous disease. Patients with high titers of antithyroid antibodies appear more prone to develop severe or sustained (irreversible) hypothyroidism. This appears to be an autoimmune mechanism rather than a direct toxicity. The diagnosis can be difficult because of the side effects of interferon, and thyroid function should therefore be assessed by routine thyroid-stimulating hormone testing before and during treatment. Thyroid dysfunction may be an example in which women are more susceptible to a side effect of alpha interferon.

OTHER IMMUNE OR AUTOIMMUNE EFFECTS

Although thyroid disease is particularly important, other autoimmune endocrine diseases have been reported to occur during interferon therapy, including diabetes, thrombocytopenia, hemolytic anemia, psoriasis, rheumatoid arthritis, systemic lupus–like syndromes, primary biliary cirrhosis, and sarcoidosis.[50]

Independent of the mild myelosuppressive effects of interferon, immune-mediated thrombocytopenia may be worsened by alpha interferon treatment.[58,59] Development of severe autoimmune thrombocytopenic purpura has been reported during interferon therapy, which ultimately responded to discontinuation of therapy along with prednisolone and immunoglobulin infusions.[60] Interferon has also been reported to induce autoimmune hemolytic anemia.[61,62]

Autoimmune endocrine disorders other than thyroiditis may be induced by interferon therapy. Diabetes mellitus may worsen or develop.[63-65] Insulin clamp data suggest that insulin resistance is the main reason for glucose intolerance observed during interferon therapy.[66]

Autoimmune arthridites, including rheumatoid arthritis, can arise during interferon therapy.[67,68] Examples of exacerbation of psoriasis with interferon therapy have been reported that can be associated with appearance of sacroileitis and arthritis.[69-72] Alpha interferon may promote the development of a systemic lupus erythematosis-like syndrome with arthralgias, rash, and anti-DNA antibodies.[73-75]

A single case report has described the onset of primary biliary cirrhosis in a 55-year-old woman without evidence of pre-existing disease receiving recombinant alpha interferon therapy for chronic hepatitis C.[76] Antimitochondrial antibodies were positive at high titer, and the liver biopsy showed a mixed picture of chronic hepatitis C and primary biliary cirrhosis. Interferon may also exacerbate existing primary biliary cirrhosis.[77]

RENAL DISORDERS

Several renal lesions, including interstitial nephritis, nephrotic syndrome, and acute renal failure, have been described in association with alpha interferon therapy of chronic hepatitis C.[78-80] The renal biopsy may show focal segmental glomerulosclerosis and tubulointerstitial nephritis. Nevertheless, alpha interferon therapy is reasonably well tolerated in hemodialyzed patients.[80,81] Renal impairment occurs in kidney transplant patients who appear to be particularly liable to rejection of the kidney leading to impaired renal function.[81]

CARDIOVASCULAR DISORDERS

Three different types of cardiovascular sequelae attributed to interferon therapy have been reported: arrhythmia, ischemic heart disease, and cardiomyopathy. These events seem rare. A small number of cases of suspected interferon-induced cardiomyopathy have been reported, but in many instances other factors such as pre-existing coronary artery disease and use of other cardiotoxic drugs may have played a contributing role in the severity of the cardiac disease.[16,82,83] In a study from Japan, 295 patients with chronic hepatitis C were carefully monitored for cardiovascular adverse events during 312 courses of interferon therapy and for 1 year thereafter.[84] Six patients developed cardiovascular adverse effects during interferon therapy and four more patients within 1 year after the end of therapy (3.2%). The adverse effects included arrhythmia (n = 4), ischemic heart disease (n = 4), and myocardial disease (n = 2). In all instances, the patient's condition improved after discontinuation of interferon and adequate therapy.

In a small prospective study from Italy, 11 patients with chronic hepatitis C treated with alpha interferon in a dose of 3 MU three times weekly for 6 months were evaluated using quantitative radionuclide angiocardiography.[85] Somewhat disturbingly, left ventricular ejection fraction decreased after 1 month of interferon therapy; a reduction of greater than 10% was observed in five patients. Three months after therapy was stopped, 9 of the 11 patients had left ventricular ejection fraction measurements that were close to the pretreatment levels. The mechanism of this finding is not clear. A reduction in left ventricular function could be critical in patients with previously reduced myocardial contractility. These results highlight the need for careful monitoring of patients with pre-existing cardiac disease during interferon therapy.

DERMATOLOGICAL SIDE EFFECTS

A variety of rashes, including erythema multiforme, have been reported to occur during interferon therapy. Pruritus can be particularly troublesome. Mild hair loss is relatively common but reversible. Local erythema at the site of injection is common. Psoriasis can develop de novo, or be aggravated, and is usually difficult to manage.[67,68,86,87] Vitiligo, perhaps as a result of induction of autoimmunity, has been reported to complicate interferon therapy for hepatitis C.[88,89] In one case, the skin lesions disappeared completely without therapy after discontinuation of interferon.[90] Lichen planus, which is associated with chronic hepatitis C virus infection independently of therapy, can be exacerbated by alpha inter-

TABLE 3. Side Effects in Interferon Trials of Hepatitis C: Meta-Analysis of Effect of Dose

Dose	Stopped Therapy	Decrease Dose	Flu-like	Depression	Alopecia	Leukopenia	Thrombocytopenia	Thyroid
3 MU for 6 mo	13/325 (4%)	14/164 (9%)	76/185 (41%)	19/274 (7%)	34/215 (16%)	21/244 (9%)	16/196 (8%)	4/190 (2%)
>5 MU for 6 mo	11/205 (5%)	10/45 (22%)	75/99 (76%)	13/134 (10%)	23/120 (19%)	13/99 (13%)	4/99 (4%)	2/99 (2%)

NOTE. Data from Poynard et al.[112]

Safety data have been collated from several large databases and therapeutic trials, and a number of retrospective surveys have reported a broad spectrum of side effects. Adverse events requiring one or more dose reductions have been reported in 10% to 15% of treated patients. Dose reductions for adverse events were required in 5% to 8%.[112] Serious and life-threatening side effects occur in 1% to 2% of patients.

There is a dose-dependent increase in the overall incidence of many, but not all, adverse events (Table 3). Monitoring requires regular clinical examinations, vital signs, urinalysis, and usually monthly measurement of serum chemistries, complete blood counts, and thyroid function tests, including thyroid-stimulating hormone levels. A serum pregnancy test should be performed before therapy, and both female and male patients should practice an adequate form of birth control during therapy.

There are important contraindications to therapy with alpha interferon (Table 4). These contraindications are based largely on the known side effects of alpha interferon. Almost all of these contraindications are relative, but the decision to use alpha interferon must be weighed carefully. Toxicity can be predicted in patients with low baseline white blood cell counts or thrombocytopenia. Hypertension, diabetes, clinically significant cardiac disease, renal, neurological, and psychiatric disease are factors that may seriously predispose patients to serious adverse events.

The risk of serious complications from alpha interferon is rare. However, serious idiosyncratic complications such as autoimmune disorders, pneumonitis, cardiac toxicity, renal disease, visual loss, or deafness can occur, and the drug must always be prescribed with caution, particularly in patients with an increased risk for these side effects.

Relatively little is known about the mechanisms of many of the side effects of alpha interferon. There are little if any differences in safety among the various forms of alpha interferon. This array of side effects indicate the importance of selecting patients for therapy and optimizing response. Careful assessment is required before treatment and monitoring is required during treatment.

TABLE 4. Relative Contraindications to Alpha Interferon Therapy

- Severe depression
- Decompensated cirrhosis (Child class B or C)
- Cirrhosis and hypersplenism
- Autoimmune hepatitis
- Hyperthyroidism
- Coronary artery disease
- Renal transplant
- Pregnancy
- Seizures
- Drugs: Sho-Saiko-to or herbal remedies
- Diabetes/hypertension and retinopathy
- Laboratory
  - Thrombocytopenia
  - Leukopenia
  - Anemia
  - High titers of autoantibodies
  - Hyperthyroidism

The combination of alpha interferon with other medications appears to lead to synergy in inducing side effects. Simultaneous therapy with herbal medications and alpha interferon has been linked to development of pneumonitis, and cardiac toxicity has been prominent in patients receiving alpha interferon and other cardiac toxins. Thus, care must be given to avoid all except necessary medications when administering alpha interferon on an elective basis for chronic hepatitis C. This caution applies particularly to chemotherapeutic agents that can be associated with cardiac and pulmonary toxicity such as methotrexate, busulfan, and cyclophosphamide.

Currently, several other investigational drugs are being assessed for the treatment of hepatitis C. Ultimately, these drugs may be used in combination with alpha interferon. The interaction of these drugs with interferon, their effects on the pharmacokinetics of interferon, and their potential for augmenting the side effects of interferon deserve careful prospective analysis.

FUTURE DIRECTIONS FOR RESEARCH

Alpha interferon has many effects on cells, inducing a variety of gene products that play a role in inducing antiproliferative and antiviral actions. Basic research on the intracellular actions of alpha interferon are important to isolate whether the beneficial effects of alpha interferon can be separated from the adverse effects. Furthermore, better knowledge of the pharmacokinetics of alpha interferon and better regimens of delivery might help to increase effectiveness without augmenting the adverse side effects of this agent.

There are many large databases on alpha interferon therapy of hepatitis C that are based on large, well-controlled clinical trials. These databases provide an invaluable resource to evaluate the frequency, timing, progression, and resolution of the adverse side effects of alpha interferon. Furthermore, these databases are likely to provide important information on predictive factors for development of side effects. Thus, the effects of age, sex, racial ethnicity, disease severity, and cofactors (such as alcohol, concurrent medications, vitamins, or smoking) on the incidence of significant side effects could be analyzed in these databases. These studies also provide the best estimates of the frequency of both moderate and severe side effects. Among patients who develop severe complications of alpha interferon therapy, careful long-term follow-up is needed to assess whether these side effects ultimately resolve.

Long-term therapy with alpha interferon is increasingly used among patients who have an excellent end-of-treatment response but who relapse when therapy is stopped. The pos-

or initiated by interferon therapy. Gastroenterology 1995;108:1942-1944.
43. Cianciara J, Laskus T. Development of transient autoimmune hepatitis during interferon treatment of chronic hepatitis B. Dig Dis Sci 1995; 40:1842-1844.
44. Ruiz-Moreno M, Rua MJ, Carreno V, Quiroga JA, Manns M, Meyer zum Buschenfelde K-H. Autoimmune chronic hepatitis type 2 manifested during interferon therapy in children [Letter]. J Hepatol 1991;12:265-266.
45. Gadano AC, Mosnier J-F, Durand F, Martinot-Peignoux M, Marcellin P, Degott C, Belghiti J, et al. α-Interferon-induced rejection of a hepatitis C virus-infected liver allograft tolerated with a low dosage immunosuppressive regimen. Transplantation 1995;59:1627-1629.
46. Magnone M, Holley JL, Shapiro R, Scantlebury V, McCauley J, Jordan M, Vivas C, et al. Interferon-alpha-induced acute renal allograft rejection. Transplantation 1995;59:1068-1070.
47. Noda K, Enomoto N, Arai K, Masuda E, Yamada Y, Suzuki K, Tanaka M, et al. Induction of antinuclear antibody after interferon therapy in patients with type-C chronic hepatitis: its relation to the efficacy of therapy. Scand J Gastroenterol 1996;31:716-722.
48. Di Cesare E, Previti M, Russo F, Brancatelli S, Ingemi MC, Scoglio R, Mazzù N, et al. Interferon-α therapy may induce insulin autoantibody development in patients with chronic viral hepatitis. Dig Dis Sci 1996; 41:1672-1677.
49. Mayet WJ, Hess G, Gerken G, Rossol S, Voth R, Manns M, Meyer zum Buschenfelde K-H. Treatment of chronic type B hepatitis with recombinant alpha-interferon induces autoantibodies not specific for autoimmune chronic hepatitis. HEPATOLOGY 1989;10:24-28.
50. Imagawa A, Itoh N, Hanafusa T, Oda Y, Waguri M, Miyagawa J-I, Kono N, et al. Autoimmune endocrine disease induced by recombinant interferon-α therapy for chronic active type C hepatitis. J Clin Endocrinol Metab 1995;80:922-926.
51. Fonseca V, Thomas M, Dusheiko G. Thyrotropin receptor antibodies following treatment with recombinant alpha-interferon in patients with hepatitis. Acta Endocrinologica 1991;125:491-493.
52. Preziati D, La Rosa L, Covini G, Marcelli R, Rescalli S, Persani L, Del Ninno E, et al. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol 1995;132:587-593.
53. Carella C, Amato G, Biondi B, Rotondi M, Morisco F, Tuccillo C, Chiuchiolo N, et al. Longitudinal study of antibodies against thyroid in patients undergoing interferon-α therapy for HCV chronic hepatitis. Horm Res 1995;44:110-114.
54. Marcellin P, Pouteau M, Renard P, Grynblat J-M, Colas Linhart N, Bardet P, Bok B, et al. Sustained hypothyroidism induced by recombinant a interferon in patients with chronic hepatitis C. Gut 1992;33: 855-856.
55. Lisker-Melman M, Di Bisceglie AM, Usala SJ, Weintraub B, Murray LM, Hoofnagle JH. Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. Gastroenterology 1992; 102:2155-2160.
56. Marazuela M, García-Buey L, González-Fernández B, García-Monzón C, Arranz A, Borque MJ, Moreno-Otero R. Thyroid autoimmune disorders in patients with chronic hepatitis C before and during interferon-α therapy. Clin Endocrinol 1996;44:635-642.
57. Baudin E, Marcellin P, Pouteau M, Colas-Linhart N, Le Floch J-P, Lemmonier C, Benhamou J-P, et al. Reversibility of thyroid dysfunction induced by recombinant alpha interferon in chronic hepatitis C. Clin Endocrinol 1993;39:657-661.
58. Stern SC, Asagba GO, Hegde UM. Prolonged thrombocytopenia following alpha-interferon for refractory immune thrombocytopenic purpura. Clin Lab Haematol 1994;16:183-185.
59. Cavanna L, Vallisa D, Berte R, Buscarini E, Fornari F, Di Stasi MC, Buscarini L. Severe immune thrombocytopenic purpura relapse after alpha-interferon in chronic myeloid leukemia, successfully treated with cyclosporine [Letter]. Am J Hematol 1994;47:255-256.
60. Dourakis SP, Deutsch M, Hadziyannis SJ. Immune thrombocytopenia and a-interferon therapy. J Hepatol 1996;25:972-975.
61. Barbolla L, Pantagua C, Outeirino J, Prieto E, Sanchez Favos J. Haemolytic anaemia to the alpha-interferon treatment: a proposed mechanism. Vox Sang 1993;65:156-157.
62. Yanaihara H, Nakazono M, Tsunoda S. A case of drug-induced immune hemolytic anemia during alpha-interferon therapy for renal cell carcinoma. [Japanese]. Nippon Hinyokika Gakkai Zasshi-Jpn J Urol 1996; 87:714-717.
63. Waguri M, Hanafusa T, Itoh N, Imagawa A, Miyagawa J, Kawata S, Kono N, et al. Occurrence of IDDM during interferon therapy fo chronic viral hepatitis. Diabetes Res Clin Pract 1994;23:33-36.
64. Fabris P, Betterle C, Floreani A, Greggio NA, De Lazzari F, Naccarat R, Cchiaramonte M. Development of type 1 diabetes mellitus dur interferon alfa therapy for chronic HCV hepatitis [Letter]. Lancet 19 340:548.
65. Foulis AK. Interferon-alpha and IDDM: comment [Letter]. Diabeto logia 1996;39:127.
66. Ishigami Y, Kanda T, Wada M, Shimizu Y. Glucose intolerance durin interferon therapy in patients with chronic hepatitis type C. Nippon Rinsho-Jpn J Clin Med 1994;52:1901-1904.
67. Nakajima M, Kubota Y, Miyashita N, Niki Y, Matsushima T, Manab T. Recurrence of sarcoidosis following interferon alpha therapy fo chronic hepatitis C. Intern Med 1996;35:376-379.
68. Nadir F, Fagiuoli S, Wright HI, Nadir A, Hopp E, Gavaler J, Van Thiel DH. Rheumatoid arthritis: a complication of interferon therap J Oklahoma St Med Assoc 1994;87:228-230.
69. Funk J, Langeland T, Schrumpf E, Hanssen LE. Psoriasis induced interferon-alpha. Br J Dermatol 1991;125:463-465.
70. Wolfer LU, Goerdt S, Schroder K, Zouboulis CC, Orfanos CE. Interferon-alpha-induced psoriasis vulgaris. Hautarzt 1996;47:124-128.
71. Lombardini F, Taglione E, Riente L, Pasero G. Psoriatic arthritis with spinal involvement in a patient receiving alpha-interferon for chronic hepatitis C. Scand J Rheumatol 1997;26:58-60.
72. Makino Y, Tanaka H, Nakamura K, Fujita M, Akiyama K, Makino I. Arthritis in a patient with psoriasis after interferon-α therapy for chronic hepatitis C. J Rheumatol 1994;21:1771-1772.
73. Mehta ND, Hooberman AL, Vokes EE, Neeley S, Cotler S. 35-year-old patient with chronic myelogenous leukemia developing systemic l erythematosus after alpha-interferon therapy [Letter]. Am J Hem tol 1992;41:141.
74. Schilling PJ, Kurzrock R, Kantarjian H, Gutterman JU, Talpaz M. Development of systemic lupus erythematosus after interferon therapy for chronic myelogenous leukemia. Cancer 1991;68:1536-1537.
75. Tolaymat A, Leventhal B, Sakarcan A, Kashima H, Monteiro C. Systemic lupus erythematosus in a child receiving long-term interferon therapy. J Pediatr 1992;120:429-432.
76. D'Amico E, Paroli M, Fratelli V, Palazzi C, Barnaba V, Callea F, Consoli G. Primary biliary cirrhosis induced by interferon-α therapy for hepatitis C virus infection. Dig Dis Sci 1995;40:2113-2116.
77. Maeda T, Onishi S, Miura T, Iwamura S, Tomita A, Saibara T, Y moto Y. Exacerbation of primary biliary cirrhosis during interfe α_{2b} therapy for chronic active hepatitis C. Dig Dis Sci 1995;40:1226-1230.
78. Coroneos E, Truong L, Olivero J. Fibrillary glomerulonephritis associated with hepatitis C viral infection. Am J Kidney Dis 1997;29:132-135.
79. Coroneos E, Petrusevska G, Varghese F, Truong LD. Focal segmental glomerulosclerosis with acute renal failure associated with alpha-interferon therapy. Am J Kidney Dis 1996;28:888-892.
80. Pol S, Thiers V, Carnot F, Zins B, Romeo R, Berthelot P, Bréchot C. Efficacy and tolerance of a-2b interferon therapy on HCV infecti of hemodialyzed patients. Kidney Int 1995;47:1412-1418.
81. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. Transplantation 1995;59:1426-1431.
82. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. Chest 1991;99:557-561.
83. Sonnenblick M, Rosenmann D, Rosin A. Reversible cardiomyopathy induced by interferon. Br Med J 1990;300:1174-1175.
84. Teragawa H, Hondo T, Amano H, Hino F, Ohbayashi M. Adverse effects of interferon on the cardiovascular system in patients with chronic hepatitis C. Jpn Heart J 1996;37:905-915.
85. Sartori M, Andorno S, La Terra G, Pozzoli G, Rudoni M, Sacchetti M, Aglietta M. Assessment of interferon cardiotoxicity with quantitative radionuclide angiocardiography. Eur J Clin Invest 1995;25:68-70.
86. Pauluzzi P, Kokelj F, Perkan V, Pozzato G, Moretti M. Psoriasis exacerbation induced by interferon-alpha. Report of two cases [Letter]. Acta Derm Venereol 1993;73:395.
87. Georgetson MJ, Yarze JC, Lalos AT, Webster GF, Martin P. Exacerbation of psoriasis due to interferon-alpha treatment of chronic active hepatitis. Am J Gastroenterol 1993;88:1756-1758.
88. Simsek H, Savas C, Akkiz H, Telatar H. Interferon-induced vitiligo in a patient with chronic viral hepatitis C infection. Dermatology 1996; 193:65-66.
89. Bernstein D, Reddy KR, Jeffers L, Schiff E. Canities and vitiligo

EXHIBIT 2

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METHODS

Selection of Patients

Adult patients were eligible for the study if they were seropositive for HCV RNA on testing with the polymerase chain reaction, had undergone a liver biopsy within one year before entry whose results were consistent with a diagnosis of chronic hepatitis, and had had elevated serum alanine aminotransferase values (more than the upper limit of normal values) for at least six months. Patients with decompensated cirrhosis,[16] serum alpha-fetoprotein concentrations of more than 50 ng per milliliter, anemia (hemoglobin concentration, less than 12 g per deciliter in women and less than 13 g per deciliter in men), human immunodeficiency virus infection, psychiatric conditions, seizure disorders, cardiovascular disease, hemophilia, poorly controlled diabetes mellitus, or autoimmune diseases were excluded, as were those who had undergone organ transplantation and those who were unable to practice contraception.

Study Design and Organization

This double-blind, placebo-controlled trial was conducted at 44 centers in the United States. The study was approved by the institutional review board at each center, and all the patients provided written informed consent. We screened 1337 patients, of whom 404 did not meet the inclusion criteria. The remaining 933 patients were randomly assigned to one of four treatment groups, which were balanced for the presence or absence of cirrhosis, pretreatment serum HCV RNA level, and HCV genotype. The analysis was based on the 912 patients who received at least one dose of medicine (21 patients were randomly assigned to a treatment group but did not receive therapy: 13 did not wish to continue, 5 did not meet the entry criteria, and 3 had adverse events before the initiation of therapy). Enrollment began in April 1996, and the trial was completed in March 1998.

The patients were randomly assigned to a treatment group as follows: recombinant interferon alfa-2b (Intron A, Schering-Plough, Kenilworth, N.J.) plus placebo for 24 weeks in the case of 231 patients and for 48 weeks in the case of 225 patients, and the combination of interferon alfa-2b and ribavirin (Rebetron, Schering-Plough) for 24 weeks in the case of 228 patients and for 48 weeks in the case of 228 patients. Interferon alfa-2b was given subcutaneously in a dose of 3 million units three times per week, and ribavirin (or matched placebo) was administered orally twice a day at a total daily dose of 1000 mg for patients who weighed 75 kg or less and 1200 mg for those who weighed more than 75 kg. Both drugs were started and stopped at the same time.

The severity of adverse events was graded as mild, moderate, severe, or life-threatening[17]; therapy was discontinued after life-threatening events. For severe adverse events other than anemia, the dose of interferon alfa-2b was reduced to 1.5 million units three times a week and the dose of ribavirin was reduced to 600 mg per day. The full dose could be resumed after the event or discontinued if the effect persisted. The dose of ribavirin was reduced to 600 mg per day in patients whose hemoglobin concentrations fell below 10 g per deciliter, and it was discontinued if the concentration fell below 8.5 g per deciliter.

The patients were evaluated as outpatients at weeks 1, 2, 4, 6, and 8 and then every 4 weeks during treatment and 4, 8, 12, and

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 WK (N=231)	48 WK (N=225)	24 WK (N=228)	48 WK (N=228)
Age — yr	45±7	44±8	44±8	44±8
Sex — M/F	154/77	150/75	148/80	152/76
Weight — kg	83.9±17.0	83.3±16.3	83.7±18.1	80.8±17.9
Serum alanine aminotransferase — no. of times upper limit of normal	4.0±2.9	3.7±2.5	4.1±2.8	3.7±2.3
Serum aspartate aminotransferase — no. of times upper limit of normal	2.9±2.3	2.7±1.7	2.9±2.2	2.7±1.7
Serum HCV RNA				
No. of copies/ml — $\times 10^{-6}$	5.0±5.0	4.8±4.6	5.1±5.3	5.7±7.5
$>2\times10^{6}$ copies/ml — no. (%)	157 (68)	162 (72)	166 (73)	152 (67)
Estimated duration of infection — yr†	18.5±9.1	18.8±9.5	18.9±9.8	19.6±9.6
Source or type of infection — no. (%)				
Transfusion	41 (18)	54 (24)	55 (24)	49 (21)
Intravenous drug use	124 (54)	115 (51)	106 (46)	127 (56)
Sporadic or unknown	66 (29)	56 (25)	67 (29)	52 (23)
Genotype — no. (%)				
1	167 (72)	162 (72)	164 (72)	166 (73)
2	38 (16)	43 (19)	29 (13)	37 (16)
3	24 (10)	19 (8)	28 (12)	23 (10)
Other	2 (1)	1 (0.4)	7 (3)	2 (1)
Knodell score‡	7.4±2.7	7.6±2.6	7.5±2.5	7.3±2.8
Cirrhosis — no. (%)	15 (6)	10 (4)	9 (4)	15 (7)
Bridging fibrosis — no. (%)	50 (22)	61 (27)	50 (22)	40 (18)

*Plus–minus values are means ±SD. Because of rounding, percentages may not total 100. None of the differences among the groups were significant.

†The duration of infection was estimated from the date of transfusion or initial exposure to other parenteral sources, and it could not be calculated for patients with sporadic infection or those in whom the source of infection was unknown.

‡Scores could range from 0 to 18, with higher scores indicating more severe abnormalities.

EXHIBIT 3

to 48 weeks increased the rate of virologic response from 31 percent to 38 percent ($P=0.05$). The rates of response at the completion of 24 weeks of therapy were almost twice as high in the combination-therapy group as in the interferon-alone group (53 percent vs. 29 percent, $P<0.001$), and the respective rates after 48 weeks of therapy were more than twice as high (50 percent vs. 24 percent, $P<0.001$). Relapse after therapy was less frequent with combination therapy (42 percent at 24 weeks and 24 percent at 48 weeks) than with interferon alone (80 percent at 24 weeks and 46 percent at 48 weeks).

In patients who were treated with interferon alone, viral clearance at week 4 was associated with a sustained virologic response, as reported previously.[25-27] However, among 51 of the 87 patients (59 percent) who were treated with combination therapy for 48 weeks and who eventually had sustained responses, HCV RNA remained detectable in serum until week 12 or 24 of therapy. Late viral clearance with a subsequent sustained response was also observed in 50 percent of patients (35 of 70 patients) who were treated with interferon and ribavirin for 24 weeks, 23 percent of those (3 of 13 patients) who received interferon alone for 24 weeks, and 52 percent of those (15 of 29 patients) who received interferon alone for 48 weeks.

Biochemical Response

The rate of sustained biochemical response was higher among patients who received interferon and ribavirin for 24 or 48 weeks than among those who received interferon alone for 24 or 48 weeks (Table 2).

The combined rates of sustained biochemical and virologic responses in the groups given interferon and ribavirin were 26 percent (60 of 228 patients) in the group treated for 24 weeks and 34 percent (77 of 228 patients) in the group treated for 48 weeks, as compared with 5 percent (12 of 231 patients, $P<0.001$) in the group treated with interferon for 24 weeks and 12 percent (27 of 225 patients, $P<0.001$) in the group treated with interferon for 48 weeks.

Normalization of serum alanine aminotransferase values was associated with undetectable levels of serum HCV RNA in most patients who had sustained virologic responses. Of 199 patients who had a sustained virologic response, 176 (88 percent) had persistently normal serum alanine aminotransferase concentrations. The mean (±SD) elevations of serum alanine aminotransferase after therapy in the remaining 23 patients (12 percent) was 1.6±0.1 times the upper limit of the normal value. Eighteen percent of patients (39 of 215) with a sustained biochemical response had persistently detectable serum HCV RNA. The proportion of patients who had sustained virologic responses among those with a sustained biochemical response was higher in the combination-therapy group as a whole (137 of 155 patients, 88 percent) than in the interferon group as a whole (39 of 60 patients, 65 percent).

Histologic Response

Pretreatment and post-treatment liver-biopsy specimens were available from 670 patients (73 percent). Histologic improvement occurred in all four groups, but it was more common in either combination-therapy group than in the interferon group that was treated for 48 weeks ($P<0.001$) (Table 3). The degree of histologic improvement, defined as a decrease in the inflammatory score of at least two points, was greatest in the group given interferon and ribavirin for 48 weeks. Of the 165 patients who had a sustained virologic response and who had pretreatment and post-treatment biopsy specimens available, 142 (86 percent) had a decrease in hepatic inflammation regardless of the treatment regimen. Inflammation also decreased in 194 of 497 patients (39 percent) who had persistent viremia at follow-up. Treatment had no effect on fibrosis.

TABLE 3. RATES OF HISTOLOGIC RESPONSE.*

VARIABLE	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 WK (N=176)	48 WK (N=158)	24 WK (N=179)	48 WK (N=157)
Change in inflammation score†				
All patients				
Percent with improvement	44	41	57	61
Mean change	−0.6	−1.0	−1.8‡	−2.4§
Patients with a response				
Percent with improvement	89	78	88	86
Mean change	−3.8	−5.2	−4.4	−4.5
Patients with a relapse or no response				
Percent with improvement	41	35	41	39
Mean change	−0.4	−0.3	−0.6	−0.5
Change in fibrosis score¶				
All patients				
Percent with improvement	11	17	16	14
Mean change	0.1	−0.1	0.0	0.0
Patients with a response				
Percent with improvement	11	26	24	16
Mean change	−0.2	−0.2	−0.2	−0.1
Patients with a relapse or no response				
Percent with improvement	11	16	12	12
Mean change	0.1	0.0	0.2	0.2

*The numbers of patients are the numbers with pretreatment and post-treatment biopsy specimens.

†Scores could range from 0 to 18, with higher scores indicating more severe abnormalities. Improvement was defined as a decrease in the inflammation score of at least two points, no change as an increase or decrease of one point, and worsening as an increase of at least two points.

‡$P=0.005$ for the comparison with 48 weeks of treatment with interferon alone.

§$P<0.001$ for the comparison with 48 weeks of treatment with interferon alone.

¶Scores could range from 0 (no fibrosis) to 4 (cirrhosis). Improvement was defined as a decrease of at least one point in the score.

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TABLE 5. RATES OF DISCONTINUATION OF TREATMENT, DOSE REDUCTIONS, AND OTHER ADVERSE EVENTS DURING TREATMENT.*

ADVERSE EVENT	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 WK (N=231)	48 WK (N=225)	24 WK (N=228)	48 WK (N=228)
	percent			
Discontinuation of treatment for any severe event	9	14	8	21
Dose reduction				
Due to anemia†	0	0	7	9
Due to other adverse events‡	12	9	13	17
Influenza-like symptoms				
Headache	63	67	63	66
Fatigue	62	72	68	70
Malaise	7	5	4	11
Myalgia	57	63	61	64
Arthralgia	27	36	30	33
Musculoskeletal pain	26	32	20	28
Fever	35	40	37	41
Gastrointestinal symptoms				
Anorexia	16	19	27	25
Dyspepsia	6	9	14	16
Vomiting	10	13	11	9
Nausea	35	33	38	46
Diarrhea	22	26	18	22
Abdominal pain	17	20	15	14
Psychiatric symptoms				
Anxiety	9	13	10	18
Impaired concentration	14	14	11	14
Depression	25	37	32	36
Emotional lability	6	8	7	11
Insomnia	27	30	39	39
Irritability	19	27	23	32
Respiratory tract symptoms				
Cough	5	9	15	14
Dyspnea	9	10	19	18
Pharyngitis	9	10	11	20
Sinusitis	7	14	9	10
Dermatologic symptoms				
Alopecia	27	28	28	32
Pruritus	9	8	21	19
Rash	9	8	20	28
Dry skin	4	8	8	15
Inflammation at injection site	10	14	13	12

*Only events that occurred in at least 10 percent of patients are included.

†The daily dose of ribavirin was reduced to 600 mg for patients with hemoglobin values below 10 g per deciliter, and treatment with ribavirin was discontinued in patients with hemoglobin values below 8.5 g per deciliter.

‡In the case of other severe events, the dose of interferon was decreased to 1.5 million units three times a week and the dose of ribavirin was decreased to 600 mg per day.

the dose of ribavirin due to anemia. Discontinuation of therapy and transfusion were necessary in one patient with a hemoglobin concentration of less than 10 g per deciliter. Reductions in the dose of ribavirin and subsequent completion of treatment did not affect the rate of sustained response. Leukocyte counts decreased in all groups during therapy, but the mean value remained within the normal range. The mean platelet counts were similar at base line and during therapy, remaining above 100×10^3 per cubic millimeter in 95 to 98 percent of all patients.

Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were more common with combination therapy than with interferon alone (Table 5). The incidence of side effects was higher after 48 weeks of treatment than after 24 weeks of treatment, regardless of the type of therapy.

The drug doses were reduced because of adverse events other than anemia in 13 percent of patients who were given interferon and ribavirin for 24 weeks and in 17 percent of those who were treated for 48 weeks. Among the patients who were given interferon alone, the dose was reduced in 12 percent of those who were treated for 24 weeks and in 9 percent of those who were treated for 48 weeks. The most frequent reason for the discontinuation of therapy in all groups was emotional disturbance — mainly depression; the frequency of cessation of treatment for depression ranged from 2 to 9 percent in the four groups.

DISCUSSION

The currently approved initial therapy for patients with chronic HCV infection consists of treatment with interferon for at least 48 weeks. The rates of sustained virologic response with this regimen are approximately 15 to 20 percent.[7-12] Our results confirm this low response rate.

We found that combination therapy with interferon and ribavirin for either 24 or 48 weeks was superior to therapy with interferon alone with respect to virologic, biochemical, and histologic end points. The higher rates of sustained virologic response were the result of higher rates of response at the end of treatment and, subsequently, lower rates of relapse. Recent reports suggest that similar sustained virologic responses are usually long-lasting (5 to 10 years) and are accompanied by progressive histologic improvement.[28,29] In our study, late clearance of HCV RNA from serum during combination therapy was also frequently associated with a sustained response. This phenomenon is uncommon in patients who are treated with interferon alone, which suggests that stopping therapy at week 12 because of persistent viremia, as recently suggested,[1,18,30] may not be appropriate in the case of therapy with interferon and ribavirin.

The beneficial effect of combination therapy also extended to subgroups of patients in whom treatment has historically been unsuccessful, such as patients with HCV genotype 1 infection, high pretreatment viral burdens, or advanced fibrosis or cirrhosis. Approximately 70 percent of U.S. patients with chronic HCV have genotype 1 infection, and such patients derived the greatest benefit from combination therapy for 48 weeks, suggesting that HCV genotyping should be considered before treatment is initiated.

EXHIBIT 3

HCV patients: assessment of RNA titer by HCV genotype. Hepatology 1997;26:Suppl:186A. abstract.
24. Bukh J, Miller RH, Purcell RH. Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. Semin Liver Dis 1995;15:41-63.
25. Hino K, Okuda M, Konishi T, Ishiko H, Okita K. Serial assay of hepatitis C virus RNA in serum for predicting response to interferon-alpha therapy. Dig Dis Sci 1995;40:14-20.
26. Kleter GE, Brouwer JT, Heijtink RA, Schalm SW, Quint WG. Detection of hepatitis C virus RNA in patients with chronic hepatitis C virus infections during and after therapy with alpha interferon. Antimicrob Agents Chemother 1993;37:595-7.
27. Orito E, Mizokami M, Suzuki K, et al. Loss of serum HCV RNA at week 4 of interferon-alpha therapy is associated with more favorable long-term response in patients with chronic hepatitis C. J Med Virol 1995;46:109-15.
28. Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 1997;127:875-81.
29. Lau DT-Y, Kleiner DE, Ghany MG, Schmid P, Hoofnagle JH. Sustained virologic response to interferon alpha (IFN-α) in chronic hepatitis C is associated with long-term histologic improvement and lack of hepatic HCV RNA. Gastroenterology 1998;114:Suppl:A1234. abstract.
30. McHutchison J, Blatt L, Sedghi-Vaziri A, Russell J, Schmid P, Conrad A. Is there an optimal time to measure quantitative HCV RNA to predict non-response following interferon treatment for chronic HCV infection? J Hepatol 1998;29:362-8.
31. Patterson JL, Fernandez-Larsson R. Molecular mechanisms of action of ribavirin. Rev Infect Dis 1990;12:1132-46.
32. Di Bisceglie AM, Conjeevaram HS, Fried MW, et al. Ribavirin as therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:897-903.
33. Dusheiko G, Main J, Thomas H, et al. Ribavirin treatment for patients with chronic hepatitis C: results of a placebo-controlled study. J Hepatol 1996;25:591-8.
34. Bodenheimer HC Jr, Lindsay KL, Davis GL, Lewis JH, Thung SN, Seeff LB. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatology 1997;26:473-7.
35. Ning Q, Brown D, Parodo J, et al. Ribavirin inhibits viral-induced macrophage production of TNF, IL-1, the procoagulant fgl2 prothrombinase and preserves Th1 cytokine production but inhibits Th2 cytokine response. J Immunol 1998;160:3487-93.

EXHIBIT 3

Diet and Chronic Liver Disease, an Updated Research Report

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The liver performs an astonishing array of vital functions in the production and use of nutrients and other chemicals. It plays a central role in sugar, fat, and protein metabolism, and is one of the key organs that incorporate nutrients into the cells of the body.

The liver is also important because it plays a significant role in the production and storage of several minerals, vitamins, starch (glycogen) and proteins needed to transport specific nutrients to various cells in the body. Therefore, it is not surprising that chronic liver disease has great impact on the body's metabolism.

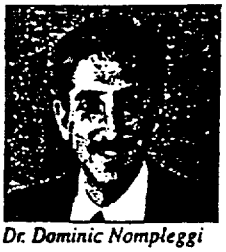
Although the normal liver has tremendous functional reserve and considerable ability to regenerate, in all patients with serious illness appropriate measures to avoid energy deficiency and to correct nutrient deficiency should be instituted without delay.

The goals of good nutritional care are always to achieve and maintain adequate nutrition by providing sufficient calories and protein. This is important because it facilitates liver cell repair and regeneration of liver tissue. This goal must be obtained without causing so-called hepatic encephalopathy.

The simplest form of hepatic encephalopathy occurs when the amount of dietary protein exceeds the ability of the liver to properly utilize the protein and therefore leads to a build up of toxins which can interfere with proper brain function. Many other factors besides total protein intake, both acute and chronic, can also contribute to the development of hepatic encephalopathy. Another important goal of good nutrition is to maintain the normal fluid and electrolyte balances in the body. In patients with advanced liver disease, diets low in salt are often prescribed in order to avoid or treat sodium retention which can lead to fluid retention and swelling of the abdomen (ascites) or the legs (peripheral edema). Therefore, adequate nutritional assessment to identify the type and degree of nutritional deficiencies is essential to any treatment plan for liver disease.

Administration of adequate calories is critical. These energy needs must be determined on an individual basis by a dietitian or physician trained in nutritional assessment and therapy. Protein should only be restricted if there is clinical evidence of encephalopathy. A mixed fuel system is essential for many reasons. Excess calories in the form of carbohydrates can lead to fat deposition in the liver and increased liver dysfunction. No more than 30% of total calories should come from fat because of the harmful effects on the cardiovascular system and because of the potential risk of immune dysfunction. When patients are not able to eat, nutrition may be maintained with the aid of a feeding tube (enteral supplementation) or by intravenous (parenteral) feeding. Calories supplied orally or enterally (into the stomach or small intestine by a tube) are safer, better tolerated and more efficiently utilized than those supplied intravenously.

A balanced diet providing sufficient calories with adequate protein and low fat is the goal of nutritional therapy in most types of diseases. Controversy exists regarding the type of protein that should be contained in the diet. Some amino acids, the basic components of protein, are believed to be less likely than others to cause encephalopathy. Vegetable and dairy protein may be better tolerated than meat protein. Even if dietary protein leads to encephalopathy, the need for protein is so important that it should only be restricted as a last resort, if medications used to correct the encephalopathy fail, and if vegetable and dairy protein have been shown to cause worsening. In these unusual circumstances, specialized solutions containing high amounts of "branched-chain" amino acids may be given intravenously or via a feeding tube to avoid protein deficiency.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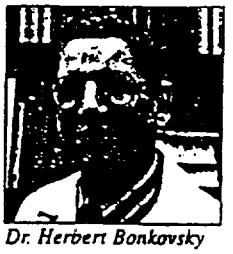
Dr. Herbert Bonkovsky

There have been more than 20 scientific studies investigating the benefits of enteral and parenteral nutritional supplementation in liver disease. Several conclusions can be drawn from these studies. First, patients who are severely ill seldom are able to meet their nutritional supplementation. Second, adverse effects of supplementation are rare. Third, nutritional supplementation can result in measurable improvements in these patients. Although, nutritional supplementation can improve quality of life, it in itself does not improve overall survival.

In today's health conscious society we are barraged with claims of health benefits for a variety of foods and dietary supplements. Keeping this in mind, one must be careful to look for scientific proof to corroborate such claims. Well-intentioned friends may provide anecdotal evidence for many kinds of "diets" or "nutritional therapies." These types of treatments must be subjected to rigorous scientific scrutiny before they can be universally recommended. For example, many herbal remedies, endorsed by some practitioners are not without risk. Plants of the Senecio, Crotalaria and Heliotopium families contain pyrrolizidine alkaloids which are toxic to the liver. Some of these components have been found in herbal "medicinal" teas such as Jamaican "bush tea" or gordolobo yerba, a tea popular in the American Southwest. Seemingly harmless therapies such as "mega-vitamin" supplements can also be harmful if they contain large doses of vitamins A and D. There are numerous studies in the literature supporting different types of vitamin or diet therapy. Most of these studies are flawed and therefore, scientists in the field have been critical of their conclusions. One also needs to be skeptical of "product claims" made by people who will financially benefit from the sales of such products and also of case reports describing the beneficial effects of a particular remedy. In the latter, one cannot be certain if the effect seen would have occurred without the treatment because no patients, with the same illness are left untreated or treated in another way, for direct comparison.

Be sensible. Be moderate. Let Solon, the 7th century Greek philosopher, be your guide: "Nothing to excess."

Patients should consult their physicians regarding the need for nutrition screening to assess the adequacy of their diet and/or the need for adjustment or supplementation. This is best accomplished by a registered dietitian working in conjunction with a physician. Early screening with appropriate interventions will decrease the likelihood of developing any nutritional deficits and help to maintain an overall sense of well-being.

EXHIBIT 3

Ask the DOC!

I have cirrhosis and chronic hepatitis. Is there any special diet I can follow to minimize damage to the liver?

In general the answer is no. We do not believe ordinary dietary factors play a role in progression of cirrhosis or hepatitis. There is no evidence that any sort of "crash" or "fad" diet can be helpful. Alcohol should be avoided. If alcohol was the cause of cirrhosis, it must be avoided entirely. Even in chronic viral hepatitis, however, alcohol taken steadily or in moderate amounts may speed up disease progression. One an argue whether "a glass of wine with dinner" is harmful, but all agree that patients with cirrhosis or active hepatitis can at most take very small amounts of alcohol. At times when cirrhosis is advanced and complications occur, physicians may restrict certain common elements of the diet. Patients who become confused when they eat too much protein ("hepatic encephalopathy") may require a low protein diet. Patients who accumulate fluid in the legs ("edema") or abdomen ("ascites"), may be started on a salt restricted diet. Except in those special cases, however, the diet should not differ from what is considered a healthy, well-rounded diet for anyone.

Are there "natural" remedies or special vitamins I can take daily to cure or improve my liver disease?

This is always a hard question to answer, and as long as medicine offers no cure for cirrhosis and few for chronic hepatitis, the question will continue to be asked. Most physicians will admit their ignorance of the large variety of "natural" or "herbal" remedies. It is not that physicians dismiss these remedies as worthless and not worthy of their attention. It is because they can find no legitimate, well-designed experiments demonstrating effectiveness of these remedies. This is in contrast to marketed and approved drugs, all of which have been studied extensively and reported in professional journals. In this circumstance, physicians act conservatively and advise patients against any unproven remedy. Most of these remedies, if they do no good, at least do no harm. This is not always the case, however. Some herbal remedies can actually cause liver disease. Even certain vitamins taken in excess (for instance, vitamin A) can cause liver disease. Fortunately, the amount of vitamin one must take for such damage to occur far exceeds the amount in a daily vitamin pill. In certain liver diseases associated with difficulty excreting bile ("cholestatic" liver disease), patients may not absorb fat-soluble vitamins (vitamins A,D,E, and K) well. Supplements of these vitamins are often given but should be prescribed by a physician.

So, the answer is, to the best of our knowledge no herbal remedy improves cirrhosis or chronic hepatitis. As to vitamins, a multivitamin a day is O.K., but more than that should be guided by your physician based on the type of liver disease you have.

EXHIBIT 3

Patient information sheet on cirrhosis:

Warning signs of liver failure:

- swollen feet
- swollen abdomen
- confusion
- progressive memory loss
- difficulty sleeping during the night and increased sleeping during the day
- vomiting blood
- passing blood, purple or black bowel movements
- yellow eyes and/or skin
- abnormal liver function:
  - "thin" blood (prolonged Protime =P.T.)
  - high bilirubin
  - low albumin
  - low cholesterol (below 100 milligrams/dl)
- low platelets
- flapping of the extended hands (asterixis)
- muscle loss

If you have cirrhosis:

1) there is a markedly increased risk of liver cancer
2) discuss with your doctor about the need for screening tests for liver cancer
   - Ultrasound of the liver (a liver scan)
   - Alpha-fetoprotein (a blood test)

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SCRIPPS MERCY HEALTHCARE
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MERCY MAGNETIC
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ENCINITAS
IMAGING CENTER
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Suite A102
Encinitas, CA 92024-1329
FAX (760) 632-5389

ADMINISTRATIVE OFFICE
5th Avenue
ox 34307
San Diego, CA 92163-4307
FAX (619) 294-8399

PROCEDURE: MAGNETIC RESONANCE IMAGING OF THE BRAIN

COMPARISON: None.

HISTORY: Headaches.

TECHNIQUE: A comprehensive examination was performed utilizing a variety of imaging planes and imaging parameters to optimize visualization of suspected pathology.

FINDINGS: There is slightly greater generalized atrophy, particularly in the frontal lobes, than is typically seen in this age group. No area of mass effect is seen.

The ventricles are normal in size and symmetric in position. The basal cisterns are normal.

CONCLUSION:

There is greater atrophy than is typically seen in this age group. Is there any history of chronic disease? Is the patient immunologically normal?

Thank you for referring this patient,

Murray A. Reicher, M.D.
ggo
Dictated: 12/16/99; Typed: 12/16/99

CC: DANIEL J BRESSLER MD

THIS REPORT IS BASED SOLELY UPON THE RADIOLOGICAL EXAMINATION.
CORRELATION WITH THE CLINICAL EXAMINATION IS ESSENTIAL.

EXHIBIT 4

John G. Rowe, M.D., Inc.
Orthopaedic Surgeon
Diplomate American Board Orthopaedic Surgeons
Fellow American Board Orthopaedic Surgeons

March 29, 2000

RE: Sara Burns
Juror#: 190604723

To Whom It May Concern:

At this time Sara Burns is currently under my care for severe Cervical Myalgia and Bilateral Hip Osteoarthrosis.

At this time I feel that she should be excused from jury duty. She is unable to sit or stand for long periods of time. In addition, I have her on medication for her cervical myalgia, which may cause her to have lethargic periods.

If you have any questions, please contact our office.

Respectfully,

John G. Rowe, M.D.
JGR:sa

EXHIBIT 5

8950 Villa La Jolla Drive, Ste. 1245, La Jolla, CA 92037
Tel: 858-625-4141 Fax: 858-625-8377 Email: DRCHIPROWE@aol.com